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PRIMARY SCLEROSING CHOLANGITIS

By

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To "the butterflies" Zahida and Zakira, my special friends in Cape Town

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ABSTRACT

Thirty six consecutive patients with primary sclerosing cholangitis (PSC), 20 males median age 42 years, were studied in order to define prognostic variables and determine the influence of surgery on outcome. Presentation was usually with insidious cholestasis or recurrent cholangitis. Twenty six patients (72 per cent) had associated inflammatory bowel disease (ulcerative colitis 20, Crohn's disease 2, unclassified 4). Thirty two patients were followed prospectively for up to nine years. Twenty three remained either stable or had slowly progressive disease. Of the remaining nine patients, seven died (five from end-stage liver failure and two from cholangiocarcinoma) and two patients underwent liver transplantation. Actuarial survival at five years was 52 per cent. A raised serum bilirubin concentration was the only variable at presentation that independently predicted a poor outcome. Cholangiograms were available for detailed assessment in thirty PSC patients. Neither the extent of biliary involvement nor the presence of surgical correctable ("dominant") strictures in the extrahepatic ductal system were of prognostic importance. Six patients who developed obstructive jaundice associated with advanced liver disease underwent surgical drainage operations for dominant biliary strictures, but this did not seem to prevent progression of the disease. Two patients who progressed to end-stage liver disease went on to liver transplantation and were alive with functioning grafts at seven and fourteen months respectively. Nine patients with asymptomatic PSC were followed prospectively for up to twelve years. None of these patients developed overt liver disease but serum bilirubin levels became mildly elevated in two patients. It is concluded that symptomatic PSC is a progressive disease with a poor prognosis. Patients with advanced liver disease due to PSC should be considered directly for liver transplantation. In contrast, asymptomatic PSC patients may remain symptom-free for many years.

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LEGENDS

CHAPTER 1: THE SYNDROME OF PRIMARY SCLEROSING CHOLANGITIS

1.1. Introduction

Primary sclerosing cholangitis (PSC) is a syndrome of unknown aetiology characterised by chronic fibrosing inflammation of the intra- and extrahepatic bile ducts. PSC is strongly associated with inflammatory bowel disease (IBD), especially ulcerative colitis (UC).[1-3] Previously considered to be a rare disease, PSC has been diagnosed much more frequently with improvements in imaging and particularly since the advent of endoscopic retrograde cholangiopancreatography (ERCP). The natural history of PSC is unpredictable although progression seems to occur in most patients. Medical therapy is unsatisfactory and end-stage liver disease due to PSC is often the reason for liver transplantation.[4] Accordingly, there has been a remarkable upsurge of interest in all aspects of this chronic liver disease during the past decade.

1.2. Clinical manifestations

PSC occurs primarily in young men. Seventy per cent of patients are male, and more than two thirds are under 45 years of age at the time of diagnosis.[1-3] The disorder usually begins insidiously with progressive fatigue, pruritus and jaundice. Bacterial cholangitis is an unusual presenting symptom of PSC, but frequently occurs in those PSC patients who have previously undergone biliary surgery or who have developed obstructing dominant strictures of the large bile ducts. Some patients with PSC may have no symptoms, and a persistly raised alkaline phosphatase is the only abnormality noted on clinical examination and routine biochemical investigations. Patients may also present initially with advanced disease that is manifested by haemorrhage from oesophageal varices, ascites, or hepatic encephalopathy.

Although the physical examination may be normal, most patients have some abnormality, most commonly hepatomegaly, jaundice, or splenomegaly. Patients with longstanding disease show evidence of chronic cholestasis, such as deep jaundice, hyperpigmentation, xanthelasmata, scratch marks, bruising, weight loss and steatorrhoea.

A cholestatic biochemical profile is present in all patients with PSC. Although the serum level of alkaline phosphatase may fluctuate, it is always raised, often markedly so. Most patients have a mild increase in the level of serum aspartate transaminase. Bilirubin values are usually raised in symptomatic patients. There are no consistently abnormal serologic markers in the serum. Tests for antimitochondrial antibody,

rheumatoid factor, smooth-muscle antibody, and antinuclear antibody are negative in more than 90 per cent of patients.[1] Tests related to copper metabolism, such as hepatic copper concentrations and serum caeruloplasmin levels, are abnormal in most patients with PSC as a consequence of cholestasis.

1.3. Radiology

Cholangiography, usually obtained by ERCP, is the key diagnostic investigation in patients with PSC. Endoscopic cannulation of the common bile duct may be difficult or impossible due to papillary fibrosis.[5] At duodenoscopy, the papilla may appear to be retracted ("tented up"), presumably as a result of fibrotic shortening of the common bile duct (author's observation). Considerable resistance may be felt as radiographic contrast material is injected into the narrowed biliary tree. In order to obtain adequate detail of the intrahepatic ducts, the catheter should be advanced deeply into the common bile duct to a position above the cystic duct, and it may be necessary to use a balloon occlusion technique when injecting contrast.[5] Cholangiography in patients with PSC carries a significant risk of bacterial cholangitis. Thus, strict endoscopic disinfection procedures should be followed, and ERCP examinations should be performed under antibiotic cover. Furthermore, radiographic contrast should only be introduced above dominant biliary strictures if facilities are available to facilitate further biliary drainage.[6]

The radiologic appearances of PSC are characteristic.[7] The intrahepatic and extrahepatic bile ducts are involved to a variable degree, with multiple strictures and areas of relative dilatation, producing a "beaded appearance" (*Figure 1.1*). These cholangiographic changes are not specific for PSC, however, and the diagnosis of PSC remains one of exclusion. The commonest causes of "secondary sclerosing cholangitis" are longstanding choledocholithiasisis and post-operative stricture with complicating recurrent bacterial cholangitis.[1] Diffuse malignant hepatobiliary infiltration may produce narrowing and deformity of bile ducts, seen at cholangiography. However, multifocal strictures and extrahepatic duct involvement are not a feature of malignant cholangiopathy (see Chapter 6). HIV-associated cholangiopathy may produce a cholangiographic picture virtually identical to PSC ("AIDS sclerosing cholangitis"). Cholangiograhic features suggestive of HIV-associated cholangiopathy include papillary stenosis and long extrahepatic bile duct strictures.[8] These apearances may be the result of recurrent biliary infection with cryptosporidium or cytomegalovirus in AIDS patients, or alternatively due to direct infection of the biliary epithelium with HIV.[8]

1.4. Hepatobiliary pathology

Although some histological lesions on liver biopsy are very suggestive of PSC, there are no absolutely unique features. The prime role of the histopathologist is to exclude other diseases and confirm that the changes present are consistent with PSC, rather than provide an unequivocal diagnosis. PSC can affect all sizes of bile ducts, from the smallest interlobular ducts to the common bile duct.[9] The **fibro-obliterative ductal lesion** is most characteristic of PSC (*Figure 1.2*), but is only found in 10 to 50 per cent of cases.[10] The interlobular ducts (less than 100μm diameter) are involved, and show periductal concentric fibrosis ("onion skinning") with a sparse mononuclear inflammatory infiltrate. Biliary epithelial atrophy results, and eventually the lumen is obliterated by fibrous tissue to form a nodular fibrous scar. Another characteristic feature is **ductopaenia** ("vanishing bile ducts"). Reduction of bile duct numbers is determined by correlating the number of interlobular bile ducts with hepatic arteries in the portal tracts. There is normally one bile duct to each hepatic artery and reduction of this ratio indicates bile duct loss.[9] Ductopaenia may however also be seen in primary biliary cirrhosis, graft versus host disease, chronic rejection, and adulthood idiopathic ductopaenia.[9] Saccular dilatation of septal bile ducts (ducts greater than 100μm diameter and lined with tall columnar epithelium) may occur. This **cholangiectasia** may occur in the absence of proximal stenosis and is thought to be part of the PSC pathogenic process.[11] A variety of nonspecific histological changes are commonly seen seen in PSC livers, including bile stasis, bile ductular proliferation and portal inflammation.[9]

The main differential diagnosis on liver biopsy is primary biliary cirrhosis (PBC), another condition showing bile duct damage and loss.[12] The inappropriate accumulation of copper-associated protein and the relative absence of Mallory bodies and of periductal granulomas favour PSC rather than PBC. Also in the hepatic histologic differential diagnosis is large extrahepatic bile duct obstruction, which produces a histological picture of swollen portal tracts with a neutrophil infiltrate and bile lakes. There may be fibrin deposition, periductal fibrosis and ductular proliferation.[13] Histology of the large extrahepatic ducts in PSC is nondiagnostic, and typically reveals generalised chronic inflammation and fibrosis.

A staging system analogous to that for PBC has been developed for PSC based on presumed pathological progression of the disease.[14] Stage 1 (portal) shows few duct lesions, portal inflammation and oedema; stage 2 (periportal) shows widespread duct lesions and portal tract expansion due to piecemeal necrosis and periportal fibrosis; stage 3 (septal) shows bridging fibrosis; and stage 4 shows biliary cirrhosis. However,

the disease is characteristically focal and appearances may vary greatly in different parts of the same liver and even in the same biopsy specimen, thus limiting the usefulness of histological staging.[9]

1.5. Inflammatory bowel disease

There is a close association between PSC and inflammatory bowel disease, especially ulcerative colitis (UC). Approximately 70 per cent of all patients with PSC have coexisting UC,[3] and PSC is the most common form of chronic liver disease found in UC, occurring in 3 - 10 per cent of patients.[15] Paradoxically, the colitis is usually total but symptomatically mild, sometimes virtually asymptomatic. Although the symptoms of UC usually develop before those of PSC, in some patients the onset of PSC may precede the symptoms of colitis by a number of years. The natural history of the hepatobiliary disease is completely unrelated to the activity, severity, or clinical course of the colitis. Interestingly, panproctocolectomy has no influence on the clinical progression or mortality of patients with PSC.[16] PSC has been reported in patients with Crohn's disease with colonic involvement, but the association is uncommon.[17]

1.6. Cholangiocarcinoma

There is a strong association between PSC and cholangiocarcinoma. Cholangiocarcinoma may arise in 10 - 15 per cent of patients with pre-existing PSC and can also present in a synchronous fashion with PSC.[18] PSC patients who appear to be at highest risk for developing cholangiocarcinoma are those with long-standing UC and cirrhotic stage PSC on liver biopsy.[18] PSC may thus be considered to be a premalignant condition of the biliary tree. Rapid clinical deterioration in a patient with PSC should alert the clinician to a possible complicating cholangiocarcinoma. Cholangiograpic features suggestive of cholangiocarcinoma include major sequential changes and impressive duct dilatation.[19] Unfortunately the cholangiographic appearances are nonspecific in many patients. Therefore, in all patients with suspicious dominant biliary strictures, brush cytology specimens should be taken at ERCP. Negative cytology is unhelpful, however, and repeat samples should be obtained from suspicious lesions. Early diagnosis is thus difficult, and approximately 10 per cent of PSC patients undergoing liver transplantation are found to have an unsuspected cholangiocarcinoma.[20] The known association of UC and bile duct cancer (estimated prevalence of 5%) may be related to underlying PSC.

1.7. Aetiology

The cause of PSC is unknown, but any hypothesis must explain the clinical associations with UC. A number of mechanisms have been postulated, including the absorption of toxic substances across the inflamed colonic mucosa, portal bacteraemia, and the increased permeation of toxic bacterial products or toxic bile acids through the inflamed colon.[21] However, there is no evidence in favour of these hypotheses. Although several viruses have been suggested as being implicated in the development of PSC, there is no direct evidence for viral infection.[22]

Recent studies suggest that genetic and immunological factors may be important. Three sets of siblings from three families have been reported with PSC and UC.[23] PSC is closely associated with the HLA B8 and DR3 antigens, which have also been associated with other auto-immune diseases, particularly immune chronic active hepatitis and coeliac disease.[24] These findings were extended by a recent report that 100 per cent of twenty nine PSC patients referred for hepatic transplantation possessed the HLA DRw52a antigen, which is on the DR B3 chain.[25] Although the 100 per cent association has not been confirmed by other workers, HLA DRw52a does appear to be most closely related to the susceptibility to develop PSC. A number of humoral and cellular abnormalities have been demonstrated in patients with PSC. Humoral abnormalities include the presence of circulating anti-colon and neutrophil cytoplasmic antibodies.[26] Several antigens appear to be common to both the colon and the biliary epithelium and it is possible that antibodies to these shared epitopes may be of importance in the disease pathogenesis.[27] PSC patients have elevated levels of immune complexes, which also appear to be poorly cleared by the reticuloendothelial system.[28,29] Moreover, there is evidence for classical complement pathway activation.[30] The cellular immune abnormalities include a decrease in suppressor T cells in peripheral blood with increased numbers of helper and suppressor cells in the portal tracts of PSC patients.[31,32] This finding is in keeping with the demonstration of the expression of HLA DR antigens on the biliary epithelial cells.[33] This aberrant expression of class II HLA antigens may enable biliary epithelial cells to present antigen to the periportal lymphocytes with subsequent activation and differentiation.

1.8. Medical therapy

Medical therapy of PSC remains unsatisfactory, and is largely aimed at relief of symptoms resulting from chronic cholestasis and treatment of complications.[34] A variety of therapies have been utilised to treat pruritus, including cholestyramine, activated charcoal, phenobarbitol, rifampicin, plasmapheresis, charcoal haemoperfusion, and ultraviolet light. Steatorrhoea should be treated with a low fat (40g per day) diet together with supplements of medium chain triglycerides. Fat soluble vitamin deficiencies should be identified and corrected by parenteral administration, where necessary. Complications of portal hypertension, such as bleeding oesophageal varices, ascites and hepatic encephalopathy, are managed in the usual manner. Complications specific to PSC include recurrent bacterial cholangitis, development of an obstructing dominant stricture of the biliary tract, and cholangiocarcinoma.

A variety of therapies have been tried in order to halt the progression of PSC, including D-penicillamine, corticosteroids, and cytotoxic agents.[35-37] However, most trials have been uncontrolled, and none of these treatments have been shown to be effective. Systemic steroid therapy may be associated with enhanced bone loss in PSC patients leading to an increased risk of developing compression fracture of the spine.[38] Topical steroids administered as a nasobiliary lavage may induce a higher incidence of bacterial cholangitis.[39] More recently there has been enthusiasm for the use of ursodeoxycholic acid and methotrexate. The rationale for using ursodeoxycholic acid in the treatment of chronic cholestatic liver disease including PSC is the replacement of the bile acid pool with a less toxic bile acid.[34] Two recent controlled clinical trials however showed that ursodeoxycholic acid therapy in PSC was associated with only minor improvement in liver function tests and no improvement in symptoms, liver histology or cholangiography.[40,41] In a controlled clinical trial, methotrexate was shown to significantly reduce serum levels of alkaline phosphatase but did not have a significant effect on serum levels of bilirubin, aminotransferases, or albumin.[42] The long-term effects of methotrexate on liver disease progression remains unknown. Of concern is the inherent hepatotoxicity leading to hepatic fibrosis that is associated with methotrexate therapy.[43] As bile duct loss is probably irreversible, any potentially effective therapy for PSC must be initiated early in the course of the disease.

1.9. References

1. LaRusso NF, Wiesner RH, Ludwig J, MacCarty R. Primary sclerosing cholangitis. *N Engl J Med* 1984;310:899-903.

2. Wiesner RH, LaRusso NF. Clinicopathologic features of the syndrome of primary sclerosing cholangitis. *Gastroenterology* 1980;79:200-206.

3. Chapman RW, Arborgh BA, Rodes JM, *et al.* Primary sclerosing cholangitis: A review of its clinical features, cholangiography and hepatic histology. *Gut* 1980;21:870-877.

4. Langnas AN, Grazi FL, Stratta RJ, et al. Primary sclerosing cholangitis: The emerging role for liver transplantation. *Am J Gastroenterol* 1990;85:1136-1141.

5. Cotton PB, Nickl N. Endoscopic and radiologic approaches to therapy in primary sclerosing cholangitis. *Semin Liver Dis* 1991;11:40-48.

6. Craig PI, Hatfield ARW. Endoscopic therapy in primary sclerosing cholangitis. *Eur J Gastroenterol Hepatol* 1992;4:284-287.

7. MacCarty RL, La Russo NF, Wiesner RH, Ludwig J. Primary sclerosing cholangitis: Findings on cholangiography and pancreatography. Radiology 1983;149:39-44.

8. Cello JP. Human immunodeficiency virus-associated biliary tract disease. *Semin Liver Dis* 1992;12:213-218.

9. Fleming KA. The hepatobiliary pathology of primary sclerosing cholangitis. *Eur J Gastroenterol Hepatol* 1992;4:266-271.

10. Barbatis C, Grases P, Shepherd HA, *et al.* Histological features of sclerosing cholangitis in patients with chronic ulcerative colitis. *J Clin Pathol* 1985;38:778-783.

11. Ludwig J, MacCarty RL, LaRusso NF, Ruud AFK, Wiesner RH. Intrahepatic cholangiectases and large-duct obliteration in primary sclerosing cholangitis. *Hepatology* 1986;6:560-568.

12. Kaplan MM. Primary biliary cirrhosis. *N Engl J Med* 1987;316:521-528.

13. Snover DC. Non-neoplastic biliary tract disease. In: Mitchell CW,ed. Biopsy *Diagnosis of Liver Disease. Baltimore: Williams and Wilkins*,1992:92-97.

14. Ludwig J, LaRusso NF, Wiesner RH. Primary sclerosing cholangitis. *Contemp Issues Surg Pathol* 1986;8:193-213.

15. Olsson R, Danielsson Å, Järnerot G, *et al.* Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis. *Gastroenterology* 1991;100:1319-1323.

16. Cangemi JR, Wiesner RH, Beaver SJ, *et al.* The effect of protocolectomy for chronic ulcerative colitis on the natural history of primary sclerosing cholangitis. *Gastroenterology* 1989;96:190-194.

17. Tobias R, Wright JP, Kottler RE, *et al.* Primary sclerosing cholangitis associated with inflammatory bowel disease in Cape Town, 1975-1981. *S Afr Med J* 1983;63:229-235.

18. Rosen CB, Nagorney DM. Cholangiocarcinoma complicating primary sclerosing cholangitis. *Semin Liver Dis* 1991;11:26-30.

19. MacCarty RL, LaRusso NF, May GR, *et al.* Cholangiocarcinoma complicating primary sclerosing cholangitis: Cholangiographic appearances. *Radiology* 1985;156:43-46.

20. Stieber AC, Marino IR, Iwatsuki S, Starzl TE. Cholangiocarcinoma in sclerosing cholangitis: The role of liver transplantation. *Int Surg* 1989;74:1-3.

21. Crippin JS, Lindor KD. Primary sclerosing cholangitis: Aetiology and immunology. *Eur J Gastroenterol Hepatol* 1992;4:261-265.

22. Minuk GY, Rascanin N, Paul RW, Lee PWK, Buchan K, Kelly JK. Reovirus type 3 infection in patients with primary biliary cirrhosis and primary sclerosing cholangitis. *J Hepatol* 1987;5:8-13.

23. Quigley EMM, La Russo NF, Ludwig J, MacSween RNM, Birnie GG, Watkinson G. Familial occurrence of primary sclerosing cholangitis and ulcerative colitis. *Gastroenterology* 1983;85:1160-1165.

24. Schrumpf E, Fausa O, Forre O, et al. HLA antigens and immunoregulatory T cells in ulcerative colitis associated with hepatobiliary disease. *Scand J Gastroenterol* 1982;17:187-91.

25. Prochazka EJ, Terasaki PI, Parks MS, Goldstein LI, Busittil RW. Association of primary sclerosing cholangitis with HLA-DRw52a. *N Engl J Med* 1990;322:1842-1844.

26. Snook JA, Chapman RW, Fleming K, Jewell DP. Anti-neutrophil nuclear antibody in ulcerative colitis, Crohn's disease, and primary sclerosing cholangitis. *Clin Exp Immunol* 1989;76:30-33.

27. Das KM, Vecchi M, Sakamaki S. A shared and unique epitope(s) on human colon, skin, and biliary epithelium detected by a monoclonal antibody. *Gastroenterology* 1990;98:464-469.

28. Bodenheimer HCJ, LaRusso NF, Thayer WR Jr, Charland C, Staples PJ, Ludwig J. Elevated circulating immune complexes in primary sclerosing cholangitis. *Hepatology* 1983;3:150-154.

29. Minuk GY, Angus M, Brickman CM, *et al.* Abnormal clearance of immune complexes from the circulation of patients with primary sclerosing cholangitis. *Gastroenterology* 1985;88:166-170.

30. Senaldi G, Donaldson PT, Magrin S, *et al.* Activation of the complement system in primary sclerosing cholangitis. *Gastroenterology* 1989;97:1430-1434.

31. Lindor KD, Wiesner RH, Katzman JA, LaRusso NF, Beaver SJ. Lymphocyte subsets in primary sclerosing cholangitis. *Dig Dis Sci* 1987;32:720-725.

32. Whiteside TL, Lasky S, Si L, Van Thiel DH. Immunologic analysis of mononuclear cells in liver tissues and blood of patients with primary sclerosing cholangitis. *Hepatology* 1985;5:468-474.

33. Chapman RW, Kelly PMA, Heryet A, Jewell DP, Fleming KA. Expression of the HLA-DR antigens on bile duct epithelium in primary sclerosing cholangitis. *Gut* 1988;29:422-427.

34. Wiesner RH. Advances in therapy for primary sclerosing cholangitis. *Eur J Gastroenterol Hepatol* 1992;4:276-283.

35. LaRusso NF, Wiesner RH, Ludwig J, MacCarty RL, Beaver SJ, Zinsmeister AR. Prospective trial of penicillamine in primary sclerosing cholangitis. *Gastroenterology* 1988;95:1036-1042

36. Burgert SC, Brown BP, Kirkpatrick RB. Positive corticosteroid response in early primary sclerosing cholangitis (abstract). *Gastroenterology* 1988;86:1037a.

37. Wagner A. Azathioprine treatment in primary sclerosing cholangitis. *Lancet* 1971;ii:633-664.

38. Hay JE, Lindor KD, Wiesner RH, Dickson ER, Krom RAF, LaRusso NF. Metabolic bone disease in primary sclerosing cholangitis. *Hepatology* 1991;14:257-261.

39. Allison MC, Burroughs AK, Noone P, Summerfield JA. Biliary lavage with corticosteriods in primary sclerosing cholangitis: a clinical, cholangiographic, and bacteriologic study. *J Hepatol* 1986;3:118-122.

40. Van Thiel DH, Wright HI, Gavaler JS. Ursodeoxycholic acid therapy for primary sclerosing cholangitis: Preliminary report of a randomised controlled trial (abstract). *Hepatology* 1992;16:62a.

41. Lo SK, Herrman R, Chapman RW, *et al.* Ursodeoxycholic acid in primary sclerosing cholangitis: A double-blind placebo controlled trial. *Hepatology* 1992; 16: 92a.

42. Knox TA, Kaplan MM. Double-blind trial of methotrexate in the treatment of primary sclerosing cholangitis (abstract). *Gastroenterology* 1991;100:761a.

43. Gilbert SC, Klintmalm G, Menter A, Silverman A. Methotrexate-induced cirrhosis requiring liver transplantation in three patients with psoriasis: A word of caution in light of the expanding use of this "steroid-sparing" agent. *Arch Int Med* 1990;150:885-891.

Figure 1.1 ERC in a patient with primary sclerosing cholangitis showing multiple strictures involving intra- and extrahepatic bile ducts with intervening dilated segments ("beaded appearance").

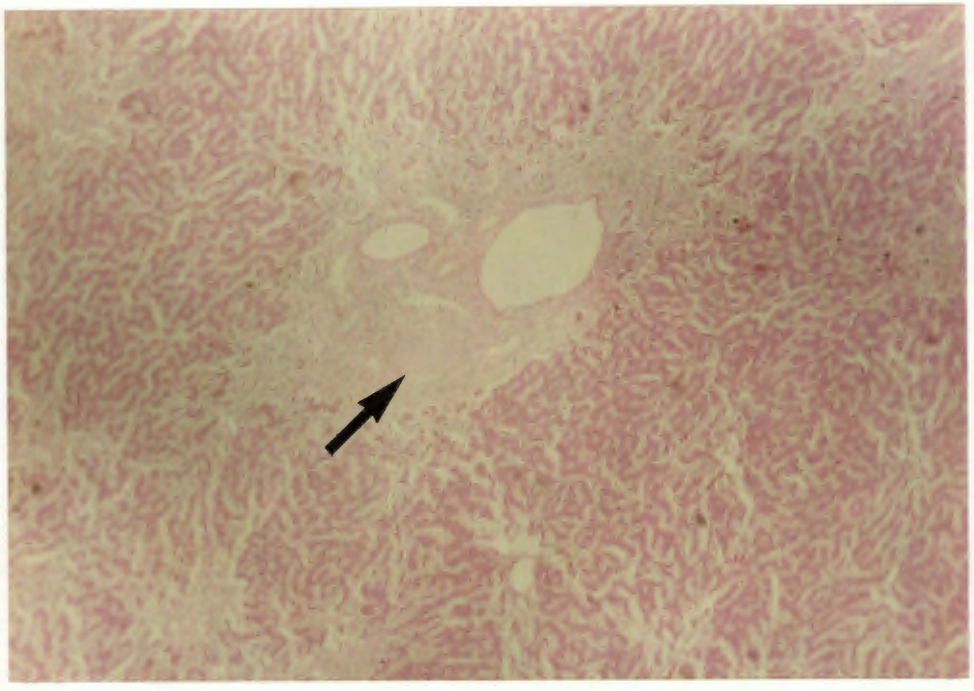

Figure 1.2 Liver biopsy specimen in a patient with primary sclerosing cholangitis showing a portal tract with dense periductal fibrosis which has resulted in disappearance of the portal bile duct (arrow). Fibrosis has extended beyond the portal tract to involve the hepatic parenchyma (Haematoxylin and eosin).

CHAPTER 2: NATURAL HISTORY AND PROGNOSTIC INDICES IN PRIMARY SCLEROSING CHOLANGITIS

2.1. Introduction

The presentation and course of patients with primary sclerosing cholangitis (PSC) are highly variable and unpredictable. Nevertheless, in most symptomatic patients, progression appears relentless with the development of jaundice, recurrent biliary sepsis, cirrhosis, portal hypertension, and liver synthetic failure.[1-3] With the advent of liver transplantation, it has become important to identify prognostic indices to predict the risk of progression to liver failure and death. These indices would be useful in deriving survival models which could be used to identify individual PSC patients at low, moderate, and high risk. A number of such prognostic models have been proposed.[4-6] Unfortunately, the studies from different units have provided conflicting results. In this chapter, the clinical presentation and outcome of 36 consecutive patients with PSC seen in Cape Town are described, with the formulation of local prognostic indices.

2.2. Patients and methods

Between January 1981 and December 1991 thirty six patients with PSC were seen and fully documented at the Liver, Gastrointestinal, and Biliary Clinics at Groote Schuur Hospital, Cape Town. The diagnosis was based on cholangiographic findings of multiple strictures of the bile ducts together with compatible clinical and biochemical features. Liver biopsy specimens were examined, and other causes of multiple bile duct strictures were excluded.

The time of diagnosis was defined as the date of the first cholangiogram. Symptoms attributable to PSC included fatigue, pruritus, jaundice, right upper quandrant pain, fever, and weight loss. Complications included portal hypertension, bleeding varices, ascites, encephalopathy, and cholangiocarcinoma. Some patients had no symptoms that could be ascribed to their liver disease; the diagnosis of PSC was made on cholangiography, which was done because of abnormal biochemical findings in patients with inflammatory bowel disease (IBD).

Liver biopsy specimens from 18 patients were reviewed without knowledge of the clinical and cholangiographic findings. The histological stage of the disease was recorded according to established criteria:[7] stage 1, cholangitis or portal hepatitis; stage 2, periportal fibrosis, piecemeal necrosis, periductal fibrosis, atrophy or

disappearance of bile ducts; stage 3, septal fibrosis or bridging necrosis, together with the features of stage 2; and stage 4, biliary cirrhosis. In addition a histological numerical score was devised using a system similar to that for chronic active hepatitis[8]. The following histological variables were assessed: paucity of ducts, periductal fibrosis, piecemeal necrosis, cholestasis, periportal inflammation, and scarring. Scoring was as follows: 0, absent; 1, mild; 2, moderate; 3, severe. Biliary cirrhosis was either absent (0) or present (1).

Long term follow-up data were available for 32 patients, the other four having been lost to local follow up due to distance of residence. The starting time for all survival analyses was the date of the cholangiogram with confirmation of diagnosis. Patient outcome was defined as either "good" or "poor". Patients with a good outcome had stable or slowly progressive disease, while those with a poor outcome had reached the end-point of either death or liver transplantation.

Presenting features were compared by Student's 't' test and Fisher's exact test. Overall actuarial survival was calculated by the Kaplan-Meier method. Prognostic indices were derived from univariate and multivariate analyses (Cox's survival analysis with correlates) using BMDP software (BMDP Statistical Software, Inc., Los Angeles, California, USA) on a mainframe computer.

2.3. Results

2.3.1. *Clinical features*

The clinical features at presentation of the thirty six patients are shown in *Table 2.1*. Twenty patients were male, and median age was 42 years (range 13-65 years). The median duration of symptoms was 14 months (range 1-84 months) before diagnosis. The commonest presenting symptoms were jaundice (67 per cent), fatigue (58 per cent), and pruritus (53 per cent). Seven patients were asymptomatic at presentation (19 per cent). Hepatomegaly was recorded in 78 per cent of patients at presentation with splenomegaly in 36 per cent. Six patients had other medical conditions - seronegative arthritis, scleroderma, immune haemolytic anaemia, pancreatitis, pyoderma gangrenosum, and hypothyroidism.

2.3.2. *Inflammatory bowel disease*

Twenty six patients (72 per cent) had associated IBD (*Table 2.2*). Twenty patients had ulcerative colitis, two had Crohn's disease, and four patients had unclassified colitis. Symptoms of IBD preceded the diagnosis of PSC by a median duration of eight years (range 43 years before -2 years after diagnosis of PSC). In the patients with ulcerative

colitis, the colitis was extensive (i.e. total or subtotal) in eighteen. The colitis was symptomatically mild (quiescent or medical control) in sixteen patients; four patients required colectomy.

2.3.3. *Hepatic histology*

Adequate liver biopsy specimens were available for detailed assessment in 18 patients. Histological staging was as follows: stage 1 (n=1), stage 2 (n=4), stage 3 (n=6), and stage 4 (n=7). Results of numerical scoring were as follows: score 0-4 (n=2), score 5-8 (n=0), score 9-11 (n=7), score 12-14 (n=8), and score 15-19 (n=1).

2.3.4. *Subsequent follow-up*

Adequate follow-up data were available for 32 patients (*Table 2.1*), the mean duration being four years (range 0.4 to 9 years). Twenty three patients either remained stable or had slowly progressive disease. Seven patients died (two from cholangiocarcinoma) and two patients underwent orthotopic liver transplantation, both of whom were alive with functioning grafts after seven and 14 months, respectively. The actuarial survival was 52 per cent at 5years (*Figure 2.1*).

2.3.5. *Prognostic indices*

Twenty three patients with a good outcome (stable or slowly progressive disease) were compared with nine patients with a poor outcome (death or liver transplant) (*Table 2.3*). Univariate analysis showed that the following variables at presentation were associated with a poor prognosis: raised serum bilirubin concentration, low serum albumin concentration, prolonged prothrombin time, presence of ascites, and stage 4 hepatic histology or with a score of greater than 11. Cox's regression (multivariate) analysis showed that a raised serum bilirubin concentration at presentation was the only variable that correlated independently with a poor prognosis.

2.4. Discussion

During the past decade, PSC has been studied intensively and a much better understanding of this syndrome has been gained, particularly in respect to its diagnostic features and natural history.[1-6] Most studies suggest an overall poor prognosis for patients with a diagnosis of PSC. The five year actuarial surval of 52 per cent of PSC patients seen in Cape Town is consistent with survival reported from other centres.[2-6] It is however the variability in the natural history on the one hand and the extremes in the treatment options (varying from conservative treatment to liver transplantation) on the other, which compounds management strategy. Therefore, various attempts have been made to identify prognostic factors which would hopefully give guidance in the

treatment of the individual patient. Several studies have used multivariate analysis to develop prognostic survival indices for PSC. This statistical procedure permits multiple clinical variables to be analysed simultaneously.[9] Helzberg *et al.*[10] showed that hepatomegaly and raised serum bilirubin concentrations were independent variables predictive of a poor outcome. Wiesner *et al.*[4] found that age, serum bilirubin concentration, haemoglobin level, hepatic histological stage, and the presence of inflammatory bowel disease were independent predictors of a poor outcome. Herrman *et al.*[6] identified age, serum bilirubin concentration, and the site of biliary involvement as indicators of poor prognosis. In patients seen in Cape Town a raised serum bilirubin concentration at presentation was the only variable that independently predicted a poor outcome, and serum bilirubin is clearly the most weighted variable. Indeed, serum bilirubin levels alone could be used as a poor man's prognostic index for PSC patients.[11] The divergent results for other prognostic indices can be explained by small patient numbers in each reported series.

Most recently, a multicentre study comprising 426 patients identified serum bilirubin, histological stage, age, and splenomegaly as independent prognostic indicators of a poor outcome in PSC.[12] This model was assessed by applying methods of statistical cross-validation and quantifying the model's reliability by estimating confidence intervals for predicting survival probabilities. A formula for the calculation of risk scores for the individual patient was devised by combining the values of the four prognostic variables with their regression coefficients. A higher score denoted a worse prognosis.

The development of multivariate statistical models in PSC is a major step in identifying individual patients at low, medium, and high risk of dying from liver disease. Such survival models may be useful for patient counselling, and also for patient stratification prior to entry into trials of drugs designed to halt disease progression. Their major application however is in recipient selection and timing of liver transplantation for PSC patients.[11] Although this represents a major advance, there are pitfalls with current survival models. They do not take into account the patient's quality of life, clearly a critical factor in the decision for transplantation candidacy in this and other cholestatic syndromes.[13] Furthermore, these models cannot forecast life-threatening events, such as a major variceal bleed or the unpredictable development of cholangiocarcinoma. Therefore, the decision and timing of therapeutic intervention with liver transplantation in PSC requires sound and individualised clinical judgement.

2.5. References

1. LaRusso NF, Wiesner RH, Ludwig J, MacCarty RL. Primary sclerosing cholangitis. *N Engl J Med* 1984;310:899-903.

2. Chapman RW, Arborgh BAM, Rhodes JM, *et al.* Primary sclerosing cholangitis: A review of its clinical features, cholangiography and hepatic histology. *Gut* 1980;21:870-877.

3. Wiesner RH, LaRusso NF. Clinicopathologic features of the syndrome of primary sclerosing cholangitis. *Gastroenterology* 1980;79:200-206.

4. Wiesner RH, Grambsch PB, Dickson ER, Ludwig J, MacCarty RL, Hunter EB. Primary sclerosing cholangitis: Natural history, prognostic factors and survival analysis. *Hepatology* 1989;10:430-436.

5. Farrant JM, Hayllar KM, Wilkinson ML, *et al.* Natural history and prognostic variables in primary sclerosing cholangitis. *Gastroenterology* 1991;100:1710-1717.

6. Herrman R, Dooley J, Sherlock S, McIntyre N. Natural history and mortality in primary sclerosing cholangitis (abstract). *Gut* 1988;29:A1430.

7. Ludwig J, Barham SS, LaRusso NF, Elveback LR, Wiesner RH, McCall JT. Morphologic features of chronic hepatitis associated with primary sclerosing cholangitis and ulcerative colitis. *Hepatology* 1981;1:632-640.

8. Knodell RG, Ishak KA, Black, *et al.* Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology* 1981;1:431-435.

9. Christensen E. Multivariate survival analysis using Cox's regression model. *Hepatology* 1987;7:1346-1358.

10. Helzberg JH, Petersen JM, Boyer JL. Improved survival with primary sclerosing cholangitis. *Gastroenterology* 1987;92:1869-1875.

11. Wiesner RH, Porayko MK, Dickson ER, *et al.* Selection and timing of liver transplantation in primary biliary cirrhosis and primary sclerosing cholangitis. *Hepatology* 1992;16:1290-1299.

12. Primary sclerosing cholangitis: Refinement and validation of survival models. *Gastroenterology* 1992;103:1893-1901.

13. Neuberger JM. Predicting the prognosis of primary biliary cirrhosis. *Gut* 1989; 30:1519-1522.

Table 2.1 Clinical features at presentation and outcome of 36 patients with primary sclerosing cholangitis. Figures are number (%) of patients unless otherwise stated

Clinical features (n = 36):	
Male:Female ratio	20:16
Median age (yr)	42
Range	13 - 65
Median duration of symptoms (mo)	14
Range	1 - 84
Jaundice	24(67)
Fatigue	21(58)
Pruritus	19(53)
RUQ pain*	14(39)
Weight loss	14(39)
Fever ("cholangitis")	6(17)
Hepatomegaly	28(78)
Splenomegaly	13(36)
Asymptomatic	7(19)
Outcome (n = 32):	
Median follow-up (yrs)	4
Range	0.4 - 9
Stable or slowly progressive disease	23
Transplant	2
Death	7‡

**RUQ, right upper quadrant*

‡ *Two patients died with cholangiocarcinoma*

Table 2.2 Associated inflammatory bowel disease. Figures are numbers of patients (%) unless otherwise stated.

Ulcerative colitis	20(77)
Crohn's disease	2(8)
Unclassified	4(16)
Median duration of IBD at time of diagnosis of PSC (years)	8
Range	-43years to +2 years
Extent of ulcerative colitis	
Total	13(65)
Subtotal	5(26)
Distal	2(11)
Activity of ulcerative colitis	
Quiescent	8(40)
Medical control	8(42)
Colectomy	4(21)

Fig 2.1 Survial by Kaplan-Meier analysis for 32 patients with PSC

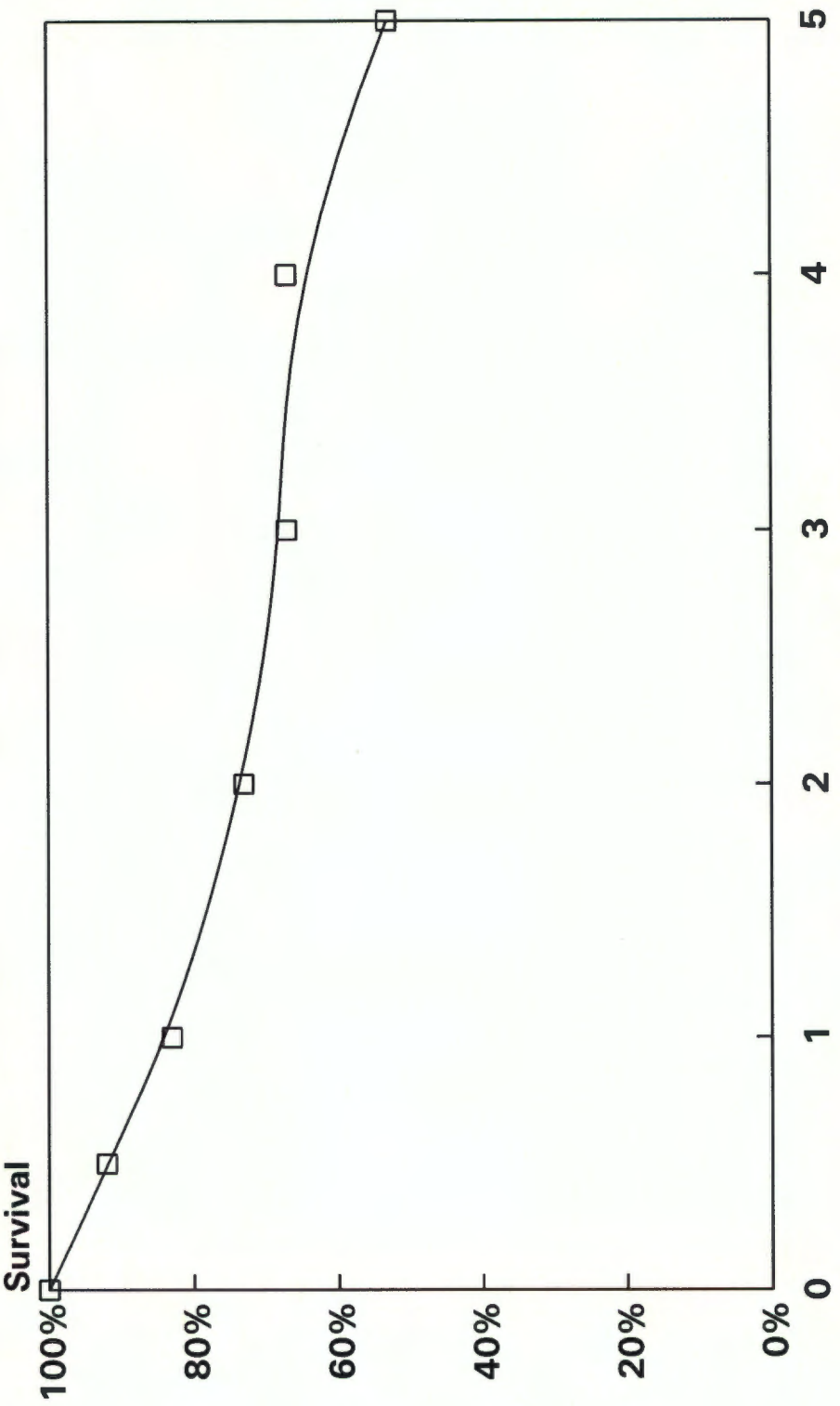

Table 2.3 Comparison of "good outcome" group with "poor outcome" group. Figures are either numbers of patients or mean (SEM).

	Good outcome (n=23)	Poor outcome (n=9)	p value
Age (years)	39(3.3)	35(3.9)	
Male:female	13:10	3:6	
Inflammatory bowel disease	19	4	
Duration of symptoms (months)	11(1-84)	8(1-60)	
Bilirubin (μmol/1)	39(8.8)	164(59)	<0.003
Albumin (g/l)	39(1.2)	32(2.7)	<0.02
INR	1.1(0.2)	1.3(.01)	<0.02
Ascites	2	4	<0.04
Liver histology			
stage 4	2/11	5/7	<0.02
score >11	3/11	6/7	<0.03

CHAPTER 3: CHOLANGIOGRAPHIC FEATURES OF PRIMARY SCLEROSING CHOLANGITIS

3.1. Introduction

Cholangiography is the the key diagnostic investigation in patients with primary sclerosing cholangitis (PSC). The characteristic radiologic findings are multifocal strictures involving the intra- and extrahepatic bile ducts with areas of relative dilatation.[1,2] Cholangiocarcinoma is the most difficult diagnosis to differentiate from PSC, and the two conditions may co-exist.[3] In contrast to its important role in diagnosis, the value of cholangiography in determining prognosis in PSC is less certain. In this study the cholangiograms of thirty PSC patients were studied. The pattern and severity of cholangiographic abnormalities were correlated with patient outcome, with particular reference to the presence or absence of dominant strictures involving the extrahepatic biliary system.

3.2. Methods

The cholangiograms of 30 PSC patients were reviewed in a blinded fashion without access to the names and clinical details of the patients. The distribution and site(s) of predominant bile duct involvement were recorded and scored as follows: 0, not involved; 1, minimal involvement; 2, moderate involvement; 3, severe involvement; and 4, non-filling. Cholangiograms were assessed for the presence of a dominant stricture at the hepatic bifurcation, common hepatic duct, or common bile duct. A "dominant" stricture was defined as a stricture which was thought to be clinically significant (i.e. potentially surgical correctable) and not necessarily the most severe biliary stricture (*Figure 3.1*). Additional features that were recorded included distortion ("pulling up") of the pancreatic duct (*Figure 3.1*), presence of a biliary stricture at the site of entry of cystic duct, side of entry of the cystic duct into the common bile duct, and features suggestive of cholangiocarcinoma. The cholangiographic findings in twenty patients from the "good outcome" group were compared with those in seven patients from the "poor outcome" group (see Chapter 2), with special reference to the presence of a surgical correctable dominant stricture of the extrahepatic bile ducts.

3.3. Results

The cholangiographic findings in the thirty patients with PSC are shown in *Table 3.1.* Thirteen patients had diffuse stricturing involving the intra- and extrahepatic bile ducts. A dominant stricture was noted involving the hepatic bifurcation/common hepatic duct in six patients, common bile duct in six, and bifurcation and common bile duct in one patient. Of the thirteen patients with dominant extrahepatic strictures, ten however also had diffuse intrahepatic involvement. Four patients had stricturing confined to the intrahepatic ducts.

Additional cholangiographic abnormalities recorded were distortion of the terminal portion of the pancreatic duct in six patients, a stricture of the CBD in relation to the cystic duct entry in eight, and a left sided cystic duct entry in nine patients. A focal stricture of the left hepatic duct with upstream dilatation was noted on the cholangiogram of one of the two patients who was found to have a cholangiocarcinoma (*Figure 3.2*).

Patient outcome in relation to the pattern of bile duct involvement is shown in *Table 3.2.* There was no significant difference in the distribution of strictures in the two outcome groups. In particular, the presence of a dominant stricture involving the extrahepatic bile ducts did not correlate with an adverse prognosis.

3.4. Discussion

The radiologic appearances of PSC are characteristic. The intra- and extrahepatic bile ducts are involved to a variable degree, with multiple strictures and areas of relative dilatation giving a "beaded appearance".[1,2] "Pseudodiverticulae" of the bile ducts are highly suggestive but not pathognomonic of PSC.[4] The observation that some patients with PSC show abnormalities in the pancreatic ductal system has not been shown to be more than coincidence.[2,5] We have confirmed the previous observation by Pitt *et al.*[6] of the terminal pancreatic duct being "pulled up" in approximately one third of cholangiograms reviewed. These changes presumably represent pancreatic duct distortion produced by fibrotic stricturing of the CBD. Another common and interesting finding was the presence of a dominant stricture of the CBD at the site of the cystic duct entry, and a left sided cystic duct entry, the latter which is also more prevalent in patients with CBD stones.[7] The significance of this finding remains obscure.

Cholangiography was unhelpful in predicting patient outcome. We found no correlation between the distribution or severity of strictures at presentation (including

the presence of a dominant stricture), and patient outcome. Of the studies on the natural history of PSC using multivariate analysis, only the one by Herrman *et al.*[8] found the site of biliary involvement to be of prognostic significance. In that study combined intra- and extrahepatic duct disease was found to be associated with a worse prognosis than intrahepatic duct disease alone. More recently, Craig *et al.*[9] studied cholangiograms in 129 patients with PSC to determine if there was a correlation between any of the findings and the prognosis of the disease. The grade, length, and extent of strictures, the degree of bile duct dilatation, and the distribution of lesions were evaluated. Using univariate analysis, survival curves were generated to test the association of these radiological findings with subsequent survival. High-grade strictures and diffuse strictures of the intrahepatic ducts were found to be indicators of a poor prognosis. Interestingly, high-grade strictures of the extrahepatic ducts were not a significant predictor of poor outcome.

PSC essentially affects the biliary system in a diffuse manner. Dominant strictures of the extrahepatic bile ducts do not appear to carry special prognostic significance. Furthermore, there is often associated diffuse severe involvement of the intrahepatic bile ducts in these patients. There thus seems to be little justification for attempting to correct such dominant strictures surgically (see Chapter 4).

3.5. References

1. Chen LV, Goldberg HI. Sclerosing cholangitis: Broad spectrum of radiologic features. *Gastrointest Radiol* 1984;9:39-47.

2. MacCarty RL, LaRusso NF, Wiesner RH. Primary sclerosing cholangitis: Findings on cholangiography and pancreatography. *Radiology* 1983;149:39-44.

3. Rosen CB, Nagorney DM. Cholangiocarcinoma complicating primary sclerosing cholangitis. *Semin liver dis* 1991;11:26-30.

4. Cotton PB, Nickl N. Endoscopic and radiologic approaches to therapy in primary sclerosing cholangitis. *Semin Liver Dis* 1991;11:40-48.

5. Palmer KL, Cotton PB, Chapman M. The pancreatogram and cholestasis. *Gut* 1984;25:424-427.

6. Pitt HA, Thompson HH, Longmire WP Jr. Primary sclerosing cholangitis: A heterogenous disease. *Ann Surg* 1982;196:127-136.

7. Bornman PC, Kottler RE, Terblanche J, *et al.* Does low cystic duct entry predispose to common bile duct stones? *Br Med J* 1988;297:31-32.

8. Herrmann R, Dooley JS, Sherlock S, McIntyre N. Natural history and mortality in primary sclerosing cholangitis (abstr). *Gut* 1988;29:A1430.

9. Craig DA, MacCarty RL, Wiesner RH, Grambsch PM, LaRusso NF. Primary sclerosing cholangitis: Value of cholangiography in determining the prognosis. *Am J Roentgenol* 1991;157:959-964.

Figure 3.1 ERC of a patient with PSC demonstrating a "dominant stricture" involving the distal CBD (large arrow). The terminal portion of the pancreatic duct appears to be "pulled up" by the strictured CBD (small arrow). This patient remained minimally symptomatic for nine years.

Table 3.1 Cholangiographic findings in 30 patients with PSC

Pattern of bile duct involvement:	
1. Diffuse intra- and extrahepatic	13
2. Dominant stricture	
a. Bifurcation/CHD*	6(5)
b. CBD**	6(5)
c. Bifurcation and CBD	1(0)
3. Intrahepatic only	4
Other associated abnormalities:	
Pancreatic duct distorted	6
Stricture related to cystic duct entry	8
Left sided cystic duct entry	9

*CHD, common hepatic duct **CBD, common bile duct

( ) = With associated diffuse intrahepatic disease

Figure 3.2 ERC of a patient with cholangiocarcinoma complicating primary sclerosing cholangitis. A tight focal stricture of the left intrahepatic duct is evident with marked upstream biliary dilatation (arrow).

TABLE 3.2 Cholangiographic findings in "good outcome" and "poor outcome" groups.

	Good outcome (n=20)	Poor outcome (n=7)
Biliary involvement:		
1. Diffuse intra- and extrahepatic	9	2
2. Dominant stricture		
a. Bifurcation/CHD	2(0)	3(2)
b. CBD	4(1)	2(2)
c. Bifurcation and CBD	1(1)	-
3. Intrahepatic only	4	-

( ) = Biliary surgery

CHAPTER 4: SURGERY FOR PRIMARY SCLEROSING CHOLANGITIS

4.1. Introduction

Medical therapy of primary sclerosing cholangitis (PSC) remains unsatisfactory and surgical options are controversial. Biliary decompression for selected patients with PSC has been advocated by a number of surgical centres.[1,2] Unfortunately, the absence of prospective controlled data makes it impossible to totally assess the impact such surgery has had on the natural history of PSC. More recently, liver transplantation has been recommended as the therapy of choice for patients with end-stage liver disease due to PSC.[3] Although early patient survival is now excellent,[4,5] the ultimate effectiveness and safety of liver transplantation for PSC is incompletely understood. This study reviews the Cape Town experience with biliary surgery and transplantation for PSC during the past decade.

4.2. Patients and methods

Six patients who had undergone biliary drainage operations for PSC in Cape Town between 1981 and 1988 were analysed and their outcome determined. The diagnosis was based on the clinical presentation, biochemical profile, and radiological features with confirmatory operative and histological findings in all patients. Surgical intervention in all six patients was indicated by progressive jaundice, with recurrent episodes of cholangitis in one patient.

The details of the operative technique employed in Cape Town have been described elsewhere,[6] and are summarised here. Exploratory laparotomy was performed with liver biopsy and exposure of the biliary tree. The gallbladder was removed, the strictured extrahepatic bile duct opened, and multiple biopsy specimens taken to exclude cholangiocarcinoma. Intra-operative dilatation of all accessible intrahepatic

duct strictures was performed using interventional radiological techniques. Following this, permanent transhepatic stenting was performed by placing a U-tube with or without a hepaticojejunostsomy (4 patients) or choledochojejunostomy (1 patient). A jejunal access loop was constructed in order to facilitate repeated post-operative percutaneous Grunzig balloon dilatations of the intrahepatic ducts, where necessary.

Two patients underwent orthotopic liver transplantation for end-stage liver disease due to PSC between 1988 and 1991. The biliary anastomosis was constructed via Roux-Y choledochojejunostomy in both recipients. Their clinical features and outcome are described.

4.3. Results

Six patients (three males, median age 38 years, range 24 - 49 years) underwent biliary drainage and duct dilatation(s) (*Table 4.1*). Four patients had associated IBD (ulcerative colitis 3, Crohn's disease 1). Median duration of symptoms before operation was 14 months (range 2 months - 4 years), and the mean serum bilirubin level at the time of surgery was 203 μmol/l (range 48 - 444). A dominant biliary stricture was present involving the distal common bile duct (CBD) in three patients, the hepatic duct bifurcation in two patients, and the bifurcation and CBD in one patient. However, associated diffuse stricturing of the intrahepatic ducts was present in all but one patient. Wedge liver biopsy showed stage 2 histology in one patient, stage 3 histology in two patients, and stage 4 histology in three patients. The patients were followed post-operatively for a median duration of 4.5 years (range 9 months - 9 years). During this period two patients developed worsening symptoms related to progressive liver disease and four patients died (one from cholangiocarcinoma). Although there was an initial improvement in the serum bilirubin levels following surgery, obstructive jaundice recurred in all patients after a median follow-up of 10

months (range 7 to 30 months). No patient from the surgical group has subsequently undergone liver transplantation.

Two patients underwent orthotopic liver transplantation for end-stage liver disease due to PSC. The first patient was a 36 year old male who initially presented with variceal bleeding, and was found to have biliary cirrhosis secondary to PSC. His post-operative course was complicated by recurrent attacks of bacterial cholangitis necessitating refashioning of the biliary anastomosis. The second patient was a 30 year old female with progressive jaundice, pruritus and fatigue due to advanced PSC. She had previously undergone panproctocolectomy for severe ulcerative colitis, as well as drainage of a hepatic abscess during pregnancy. Her post-operative course was complicated by cytomegalovirus hepatitis and ductopaenic rejection requiring FK 506 immunosuppressive therapy. Both patients were alive with functioning grafts at seven and fourteen months respectively.

4.4. Discussion

A variety of operations have been proposed in order to facilitate biliary drainage in patients with PSC. Historically, operative dilatation of the major bile ducts was performed with prolonged external T-tube drainage. Unfortunately, the results with this operation were poor.[7] This led some surgeons to institute a more aggressive approach at biliary decompression in selected patients with PSC. Cameron *et al.*[1] advocated resection of the hepatic duct bifurcation and dilatation of intrahepatic ducts followed by prolonged transhepatic stenting. Favourable results were reported in non-cirrhotic patients with dominant strictures at the hepatic duct bifurcation.[1] A simpler procedure was employed in Cape Town. This entailed biliary-enteric drainage of extrahepatic strictures with operative and, where necessary, repeated postoperative percutaneous dilatation of intrahepatic strictures with invasive radiological techniques.[6] Although there was temporary relief of jaundice and pruritus in some patients, ultimate

outcome was not improved. The unfavourable experience in Cape Town can be explained by advanced chronic liver disease and associated diffuse intrahepatic stricturing in the patients operated on. Although patient numbers were small, it is felt that ductal surgery is not indicated in this subgroup, even in the presence of a surgical correctable stricture. The favourable results with biliary surgery reported by others may relate to patients being operated on at an earlier stage of the disease. However, it is unlikely that the natural history of this diffuse and progressive disease is altered by surgical intervention. Furthermore, these patients are at an increased risk for the development of bacterial cholangitis,[3] and future liver transplantation may be compromised.[8] It may be better to intervene endoscopically if possible, and to temporise until the patient becomes a candidate for liver transplantation.[9,10]

Liver transplantation is now regarded by many as the therapy of choice for patients with end-stage liver disease due to PSC.[3,11] Good transplant centres report survival rates of over 85 per cent at three years.[4,5] There are however several considerations (apart from variability of disease progression and prior biliary surgery) when selecting PSC patients for liver transplantation. These include the frequent fibrotic involvement of the extrahepatic ducts (necessitating choledochojejunostomy), previous operations for IBD, and the unpredictable development of cholangiocarcinoma.[8] The ultimate effectiveness of liver transplantation for PSC is incompletely understood. There is a high complication rate following transplantation for PSC, and the retransplantation rate is increased.[12] Diffuse biliary stricturing has been found to occur more frequently in PSC patients undergoing liver transplantation.[13] While these findings suggest recurrence of PSC, there may be other factors such as reflux cholangitis (related to the choledochojejunostomy) and chronic rejection.[3] Our one transplant recipient required refashioning of the biliary anastomosis and the other recipient developed ductopaenic rejection requiring FK 506, both recognised complications of transplantation for this disorder.[13,14]

4.5. References

1. Cameron JL, Pitt HA, Zinnen MJ, *et al.* Resection of hepatic duct bifurcation and transhepatic stenting for primary sclerosing cholangitis. *Ann Surg* 1988;207: 614-622.

2. Lillemoe KD, Cameron JL. Surgical approaches to primary sclerosing cholangitis. *Semin Liver Dis* 1991;11:49-55.

3. Wiesner RH. Advances in therapy for primary sclerosing cholangitis. *Eur J Gastroenterol Hepatol* 1992;4:276-283.

4. Langnas AN, Grazi FL, Stratta RJ, *et al.* Primary sclerosing cholangitis: The emerging role for liver transplantation. *Am J Gastroenterol* 1990;85:1136-1141.

5. McEntee G, Wiesner RH, Rosen C, Cooper J, Wahlstrom E. A comparative study of patients undergoing liver transplantation for primary sclerosing cholangitis and primary biliary cirrhosis. *Trans Proc* 1991;23:1563-1564.

6. Krige JEJ, Terblanche J, Harries-Jones EP, Bornman PC. Primary sclerosing cholangitis: Biliary drainage and duct dilatation. *Br J Surg* 1987;74:54-57.

7. Pitt HA, Thompson HH, Tomkins RK, *et al.* Primary sclerosing cholangitis: Results of an aggressive surgical approach. *Ann Surg* 1982;196:259-268.

8. Ismail T, Angrisani L, Powell JE, *et al.* Primary sclerosing cholangitis: Surgical options, prognostic variables and outcome. *Br J Surg* 1991;78:564-567.

9. Cotton PB, Nickl N. Endoscopic and radiologic approaches to therapy in primary sclerosing cholangitis. *Semin Liver Dis* 1991;11:40-48.

10. Craig PI, Hatfield ARW. Endoscopic therapy in primary sclerosing cholangitis. *Eur J Gastroenterol Hepatol* 1992;4:284-287.

11. Robson SC, Kahn D, Krige JEJ, Lemmer ER. Primary sclerosing cholangitis (letter). *S Afr Med J* 1991;80:59-60.

12. Catalano MF, Ferguson DR, Carey W, Broughan T, Vogt D. Liver retansplantation rate is higher in primary sclerosing cholangitis (abstract). *Hepatology* 1992;16(suppl):275A.

13. Letourneau JG, Day DL, Hunter DW, *et al.* Biliary complications after liver transplantation in patients with pre-existing primary sclerosing cholangitis. *Radiology* 1988;167:349-351.

14. Crippin JS, Carlen SL, Goldstein RM, Husberg BS, Klintmalm G. Ductopaenic rejection: Increased risk in primary sclerosing cholangitis (abstract). *Hepatology* 1992;16(suppl):276A.

Table 4.1 Details of patients undergoing biliary drainage and duct dilatation(s)

Patient	Sex	Age *(years)*	Pre-operative Duration of symptoms	Bilirubin *(0-17μmol/l)*	Dominant biliary stricture	Liver histology	Operative procedure*	Follow-up	Clinical status
1.	M	24	18 months	48	distal CBD**	stage 4	CBDE & dilatation HJ, stent	9 years	Worsening symptoms
2.	M	35	2 months	91	bifurcation, distal CBD	stage 2	CBDE & dilatation‡ HJ, stent	5 years	Worsening symptoms
3.	M	28	3 years	444	bifurcation**	stage 3	CBDE & dilatation stent	9 months	Died
4.	F	41	4 years	374	bifurcation**	stage 4	CBDE & dilatation‡ HJ, stent	2 years	Died
5.	F	46	10 months	153	distal CBD**	stage 3	CBDE & dilatation CJ, stent	4 years	Died *(Cholangio carcinoma)*
6.	F	49	9 months	106	distal CBD**	stage 4	CBDE & dilatation‡ HJ, stent	7 years	Died

**CBDE, common bile duct exploration HJ, hepaticojejunostomy CJ, choledochojejunostomy*

***Associated diffuse intrahepatic involvement ‡ Repeated percutaneous Grunzig balloon dilatations post-operatively via access loop*

CHAPTER 5: ASYMPTOMATIC PRIMARY SCLEROSING CHOLANGITIS IN ASSOCIATION WITH INFLAMMATORY BOWEL DISEASE

5.1. Introduction

The widespread availability of endoscopic retrograde cholangiography (ERC) has led to a greater number of patients with primary sclerosing cholangitis (PSC) being diagnosed at an early asymptomatic stage. The diagnosis is made incidentally when a persistently raised alkaline phosphatase is discovered, usually in a patient with ulcerative colitis.[1] Liver biopsy may be entirely normal or show portal inflammation, a histological picture previously termed "pericholangitis".[2,3] There has been controversy as to the proportion of asymptomatic patients who will progress, and the rate of progression to symptomatic chronic liver disease and liver failure. This is of importance in deciding whether asymptomatic patients should be offered entry into clinical trials of remittive drugs. Prognostic indices are applicable to patients with clinically symptomatic disease but are of limited use in the subpopulation identified by incidental biochemical results.

5.2. Patients and methods

All patients with asymptomatic PSC seen at the Inflammatory Bowel Disease (IBD) Clinic in Cape Town between January 1975 and December 1991 were studied. The diagnosis was suspected by the finding of a persistently raised alkaline phosphatase (to more than twice the normal level) in a patient with IBD, and confirmed at ERC. Patients were followed prospectively and monitored for biochemical or clinical evidence of disease progression. The cholangiograms were reviewed and the distribution and severity of biliary strictures were recorded.

5.3. Results

Nine patients, five males median age 34 years (range 18 - 53 years), were identified (*Table 5.1*). At diagnosis patients had a mean (SEM) serum alkaline phosphatase of 300 (11.9) iu/l (normal 30 - 115) and serum aspartate transaminase of 54.2 (5.5) iu/l (normal 0 - 40). Associated IBD comprised ulcerative colitis (7), Crohn's ileocolitis (1), and unclassified colitis (1). Associated ulcerative colitis was invariably extensive but symptomatically mild. One patient required panproctocolectomy for colonic dysplasia. The frequency of asymptomatic PSC in patients with ulcerative colitis was approximately 0.6 per cent. Mean duration of IBD before diagnosis of PSC was seven years (range 1 - 24 years). ERC demonstrated minimal stricturing confined to the intrahepatic biliary tree in three patients , diffuse stricturing affecting both the intra- and extrahepatic bile ducts in five patients (*Figure 5.1*), and a dominant stricture involving the common hepatic duct in one patient. Liver biopsy was performed in two patients. Histology showed mild condensation of periportal fibrous tissue in the one patient and "pericholangitis" in the other patient. None of these patients developed overt liver disease during a mean follow-up period of 5.3 years (range 1 - 12 years). Serum bilirubin levels became mildly elevated (to 22μmol/l and 33μmol/l respectively) in two patients.

5.4. Discussion

Some patients with PSC have no symptoms referrable to their liver disease. The proportion of asymptomatic patients in published series varies from 16 - 25 per cent.[4-6] In the natural history study performed in Cape Town, 20 per cent of the PSC patients were asymptomatic at presentation (see Chapter 2). The frequent detection of PSC patients during an asymptomatic phase relates to the widespread availability of ERC together with an increased awareness of the association of PSC with IBD. The diagnosis is suspected by the finding of a persistently raised alkaline phosphatase in a patient with ulcerative colitis and confirmed at ERC.[7] Previously the term

"pericholangitis" was synonymous with asymptomatic involvement of the liver in patients with IBD.[2,3] However, it has become clear that most patients with histological pericholangitis, defined as an inflammatory portal reaction with periductular inflammation and fibrosis, will have cholangiographic appearances of PSC.[8] A minority of patients with ulcerative colitis will have persistently abnormal liver function tests together with histological appearances such as concentric fibrosis, but have normal bile ducts at cholangiography. The term "small duct primary sclerosing cholangitis" has been proposed to replace the term "pericholangitis" in this group of patients, as the evidence suggests that these conditions are all part of the same disease spectrum.[9]

The outcome for patients with asymptomatic PSC has not been clearly established. Chapman *et al.*[10] initially suggested that PSC may remain asymptomatic for many years. They reported on three cases of asymptomatic PSC with extensive cholangiographic abnormalities who remained well for up to 15 years. Follow-up liver biopsy in two showed no evidence of histological progression. Heltzberg *et al.*[6] described 13 PSC patients who were asymptomatic at presentation and remained so during a mean follow-up period of 56 months. In addition, Aadland *et al.*[11] reported that 27 asymptomatic or minimally symptomatic patients followed for a mean of 4.4 years showed no evidence of disease progression. This is in contrast to findings by Porayko *et al.*[12] who found that 76 per cent of 45 asymptomatic patients had clinical or laboratory evidence of disease progression during a median follow-up of 75 months and 31 per cent developed liver failure resulting in death or referral for liver transplantation. These results were in agreement with those of Herrman *et al.*[13] who reported on 14 asymptomatic patients; nine (64 per cent) showed clinical progression over a mean follow-up period of three years.

This study shows that the outcome for asymptomatic PSC patients is clearly better than for those who are already symptomatic.[14] This favourable outcome can be explained

by the design of the study. Patients attending the IBD Clinic in Cape Town were actively screened for abnormal liver function tests and then submitted for ERC examination. Thus, asymptomatic patients were detected at an earlier stage in their disease process. Of interest however was that cholangiography in these patients did not necessarily reflect early disease; some patients had diffuse severe stricturing of the biliary tree, and one patient had a dominant stricture of the extrahepatic bile duct. Inclusion of these asymptomatic patients in clinical trials of drugs designed to reduce disease progression may falsely skew overall results. They should therefore be stratified prior to entry into such trials. It seems likely however that many of these patients will eventually progress to symptomatic chronic liver disease. Further follow-up of this important subset of patients is thus needed.

5.5. References

1. Chapman RW. Aetiology and natural history of primary sclerosing cholangitis: A decade of progress? *Gut* 1991;32:1433-1435.

2. Mistilis SP. Pericholangitis and ulcerative colitis: I Pathology, aetiology and pathogenesis. *Ann Intern Med* 1965;63:1-16.

3. Mistilis SP, Skyring AP, Goulston SJM. Pericholangitis and ulcerative colitis: II Clinical aspects. *Ann Intern Med* 1965;63:17-26.

4. Farrant JM, Hayllar KM, Wilkinson ML, *et al.* Natural history and prognostic variables in primary sclerosing cholangitis. *Gastroenterology* 1991;100:1710-1717.

5. Wiesner RH, Grambsch PM, Dickson ER, *et al.* Primary sclerosing cholangitis: Natural history, prognostic factors and survival analysis. *Hepatology* 1989;10: 430-436.

6. Heltzberg JH, Petersen JM, Boyer JL. Improved survival with primary sclerosing cholangitis: A review of clinicopathologic features and comparison of symptomatic and asymptomatic patients. *Gastroenterology* 1987;92:1869-1875.

7. Tobias R, Wright JP, Kottler RE, *et al.* Primary sclerosing cholangitis associated with inflammatory bowel disease in Cape Town, 1975-1981. *S Afr J Med* 1982; 63:229-235.

8. Shepherd HA, Selby WS, Chapman RW, *et al.* Ulcerative colitis and liver dysfunction. *Quart J Med* 1983;52:503-513.

9. Ludwig J. Small-duct primary sclerosing cholangitis. *Semin Liver Dis* 1991;11: 11-17.

10. Chapman RW, Burroughs AK, Bass NM, Sherlock S. Longstanding asymptomatic primary sclerosing cholangitis: Report of three cases. *Dig Dis Sci* 1981;26:778-782.

11. Aadland E, Schrumpf E, Fausa O, *et al.* Primary sclerosing cholangitis: A long-term follow-up study. *Scand J Gastroenterol* 1987;22:655-664.

12. Porayko MK, Wiesner RH, Larusso NF, *et al.* Patients with asymptomatic primary sclerosing cholangitis frequently have progressive disease. *Gastroenterology* 1990;98:1594-1602.

13. Herrmann R, Dooley J, Sherlock S, McIntyre N. Progression of asymptomatic primary sclerosing cholangitis. *J Hepatol* 1988;7(suppl):S39.

14. Lemmer ER, Robson SC, Wright JP, Girdwood AH, Bornman PC. Asymptomatic primary sclerosing cholangitis in association with inflammatory bowel disease. *J Clin Gastroenterol* 1993;16(in press).

Table 5.1 Clinical details of nine patients with asymptomatic primary sclerosing cholangitis

Patient	Sex/Age (years)	IBD type*	UC extent	UC activity	Duration pre PSC(yrs)	ALP (0-40iu/l)	Cholangio-graphy	Follow-up since diagnosis (years)	Current bilirubin (0-17μmol/l)
1	M 28	UC	total	mild	4	167	diffuse	5	5
2	F 28	UC	distal	quiescent	7	553	mild diffuse	5	17
3	M 45	UN	-	-	13	217	intrahepatic	3	6
4	F 40	UC	total	moderate	2	506	diffuse	12	5
5	M 42	UC	subtotal	moderate	1	383	mild untra-hepatic	1	15
6	M 24	CD	-	-	5	115	dominant stricture CHD*	5	4
7	F 18	UC	total	quiescent	4	246	mild intra-hepatic	2	5
8	M 53	UC	total	quiescent	24	280	diffuse	3	22
9	M 34	UC	total	colectomy (dysplasia)	14	232	severe diffuse	12	33

** CHD, common bile duct*

**UC = Ulcerative colitis CD = Crohn's disease UN = unclassified colitis*

Figure 5.1 ERC of patient 4 showing classical changes of primary sclerosing cholangitis with diffuse stricturing affecting both the intra- and extrahepatic bile ducts. This patient has remained completely asymptomatic for twelve years.

CHAPTER 6: MALIGNANT CHOLANGIOPATHY MIMICKING PRIMARY SCLEROSING CHOLANGITIS

6.1. Introduction

Hepatobiliary infiltration with neoplastic/malignant cells may produce a clinical and cholangiographic picture similar to that of primary sclerosing cholangitis (PSC). This may be due to biliary compression by tumour cells, or due to bile duct injury with scarring. This chapter documents three cases of malignant obstructive cholangiopathy seen in Cape Town, with a review of the literature. Malignant infiltration of the hepatobiliary system should be considered in the differential diagnosis of PSC where atypical presentations are noted.

6.2. Case reports

6.2.1. *Idiopathic hypereosinophilic syndrome*

A 16 year old boy was referred for investigation of a pyrexia of unknown origin associated with eosinophilia and abnormal liver tests. There was a five week history of a febrile illness with associated lethargy, backache, dyspepsia, intermittent diarrhoea, joint pains and weight loss. Clinically he was ill and pyrexial with mild lymphadenopathy and jaundice. There was a 3cm firm hepatomegaly (15cm span) and a 2cm splenomegaly. Colonoscopy demonstrated friable oedematous mucosa extending from the rectum to proximal transverse colon and histology revealed non-specific colitis with incipient crypt abscesses. Special investigations revealed anaemia, leucocytosis with a marked eosinophilia of 28 000/mm^3, and biochemical tests confirmed severe cholestasis. Anti-nuclear and anti-smooth muscle antibodies were present in low titre. Repeated blood, urine and stool cultures, and serology for all potentially relevant infections, including human immunodeficiency virus (HIV), were negative. Computed tomography (CT) showed an enlarged liver with features suggestive of periportal

oedema, but no intrahepatic biliary dilatation. Endoscopic retrograde cholangiography (ERC) demonstrated marked irregularity of the intrahepatic ducts suggestive of PSC (*Figure 6.1*). Initial liver histology demonstrated eosinophilic infiltration around portal tracts and the bile ducts, but no periductal fibrosis to suggest PSC. The initial clinical diagnosis was considered to be idiopathic hypereosinophilic syndrome with gastrointestinal involvement and obstructive cholangiopathy. The patient failed to respond satisfactory to steroid therapy, and his course was marked by progressive eosinophilia with recurrent fever, vasculitic skin lesions, worsening diarrhoea and mental confusion. Induction chemotherapy as for eosinophilic leukaemia was commenced, but this was complicated by cerebellar toxicity and terminal gastrointestinal haemorrhage. At postmortem, histology revealed dense circumferential fibrosis of large bile ducts, hepatic fibrosis and cholestasis. There was a chronic inflammatory cell infiltrate of the colon with scarring, but no eosinophils were seen. Review of marrow trephine biopsies provided convincing evidence of evolution into eosinophilic leukaemia.

6.2.2. *Langerhans-cell histiocytosis*

A 10 year old boy presented with progressive pulmonary disease associated with chronic liver disease and portal hypertension. Hepatosplenomegaly had been noted 4 years previously and was thought to be compatible with congenital hepatic fibrosis after examination of liver histology. This young patient developed progressive splenomegaly and pancytopaenia over the next three years. Bone marrow trephine biopsies were consistent with hypersplenism. Two years after initial presentation, he developed a persistent cough, and chest radiography demonstrated bilateral infiltrates. Atypical mycobacteria were cultured from sputa, but response to antituberculous therapy was poor. A few months before admission he developed progressive fatigue, weight loss, jaundice, steatorrhoea and worsening cough. Clinically, he appeared chronically ill with pallor and jaundice. A persistent low grade fever was noted. Digital clubbing,

generalised lymphadenopathy and spider naevi were also documented. Chest auscultation revealed soft basal crackles. A shrunken liver with a total vertical span of 8cm, minimal ascites and massive splenomegaly, which extended into the right iliac fossa, were present. Stools tested positive for occult blood. Special investigations revealed pancytopaenia and marked cholestasis; steatorrhoea was confirmed on a three day stool collection. There was no biochemical evidence of diabetes insipidus. Lung functions demonstrated non-obstructive reduction in volumes with a decreased transfer factor. Sputum examination was unhelpful. Chest radiography showed diffuse inhomogeneous opacification with small cystic changes in both lungs and a basal honeycomb pattern. No lytic bone lesions were seen. Abdominal CT demonstrated massive splenomegaly, a small lobulated liver and ascites. No biliary duct dilatation or focal hepatic lesions were seen. He was subjected to open lung biopsy and repeat liver biopsy. Histopathology revealed pulmonary Langerhans-cell histiocytosis with characteristic markers, including T6 antigen and S-100 protein. Liver histology showed extrahepatic cholestasis and septal fibrosis but no evidence of active histiocytosis. ERC was not performed as his immediate post-operative course was complicated by a major variceal bleed requiring urgent sclerotherapy. He deteriorated rapidly and died shortly thereafter.

6.2.3. *Metastatic ovarian adenocarcinoma*

A 39 year old woman was referred with a diagnosis of end-stage PSC for liver transplantation. She had been well until 2 years before admission when she had experienced severe left iliac fossa pain. Hysterectomy and bilateral salpingo-oophorectomy were performed for a fibroid uterus and what was considered to be bilateral cystadenomas of the ovaries. Nine months prior to admission at Groote Schuur Hospital she developed worsening right upper quadrant pain with itching, nausea, protracted vomiting and a 20kg weight loss. ERCP at another hospital was suggestive of PSC. Clinically, she was ill and jaundiced with profuse vomiting. There

was foetor hepaticus with asterixis. A tender 3cm hepatomegaly (span of 14cm) was noted but the spleen was impalpable. Biochemistry showed severe cholestasis. Viral serology, autoantibodies and tumor markers were negative. CT revealed a normal sized liver with multiple low density tubular structures within it, but no mass lesions. There was mild dilatation of the extrahepatic bile duct. Minimal ascites was demonstrated and there was no evidence of adenopathy. ERC demonstrated diffuse narrowing and irregularity of the intrahepatic bile ducts with involvement of the hepatic duct bifurcation. The extrahepatic bile duct was not involved (*Figure 6.2*). At laparotomy, metastatic cystadenocarcinoma with gross involvement of the liver, mesentery, omentum and porta hepatis was present. Tumour cells showed strong positivity for carcino-embryonal antigen. Review of the initial ovarian histology confirmed mucinous cystadenocarcinoma.

6.3. Discussion

Malignant hepatobiliary infiltration may produce a cholangiographic picture similar to that of primary sclerosing cholangitis (PSC). Cholangiocarcinoma is the tumour that is most commonly mistaken for PSC. This tumour may indeed complicate PSC in five to ten per cent of patients, and both conditions may present simultaneously.[1] Cholangiocarcinoma complicating PSC is heralded by rapid clinical deterioration with progressive jaundice, weight loss and abdominal discomfort. The tumour is usually detected at an advanced stage and the prognosis is poor.[2]

This chapter describes three cases of malignant obstructive cholangiopathy mimicking PSC.[3] The first report describes a 16 year old boy with idiopathic hypereosinophilic syndrome (HES) who presented with colitis and obstructive cholangiopathy, closely resembling PSC with associated ulcerative colitis. ERC demonstrated marked irregularity of the intrahepatic bile ducts. Initial eosinophilic infiltration of the liver was followed by fibrotic scarring involving both intra- and extrahepatic bile ducts.

Post-mortem histology of the colon favoured chronic idiopathic inflammatory bowel disease rather than eosinophilic gastroenteritis, but the picture may have been modified by prior chemotherapy. HES is considered to be a multisystem idiopathic disorder characterised by prolonged eosinophilia with organ dysfunction. Hepatic involvement occurs in approximately 30 per cent of cases, and usually consists of periportal infiltration by eosinophils.[4] However, Scheurlen *et al.*[5] have recently reported a case of HES with radiologically and histologically confirmed involvement of the bile ducts (*Table 6.1*). Their patient had endoscopically proven colitis with extreme eosinophilia, and went on to develop obstructive cholangiopathy and recurrent angioedoma. Subsequently a good response to hydroxyurea therapy was documented. Although eosinophilia has been reported in association with PSC,[6] the extreme eosinophilia with organ dysfunction pointed to the correct diagnosis, as in this patient.

The second report describes a 10 year old boy with Langerhans-cell histiocytosis (LCH, histiocytosis X) who presented with hepatic fibrosis, and later developed active lung disease with progressive hepatobiliary involvement. Although ERC was not performed in this instance, liver biopsy demonstrated involvement of intrahepatic intralobular bile ducts together with histological evidence of extrahepatic large duct obstruction. LCH is characterised by infiltration of various organs by histiocytes or dendritic cells recognised by specific Birbeck granules on electron microscopy or T6 antigenic markers.[7,8] The course is highly variable with remissions, but residual disability may result from fibrotic scarring. Thompson *et al.*[9] reported on three patients with biopsy proven histiocytosis who developed a clinical and pathological picture compatible with PSC (*Table 6.1*). They showed that the abnormal cell types may be absent from liver biopsy specimens which may merely show fibrotic scarring. The authors concluded (probably erroneously) that histiocytosis may be an underlying cause of PSC in some instances. Case reports of portal hypertension in infants and children with histiocytosis during the 1970's (ERC examinations were not performed) probably described the

same condition.[10] In this case the young age at presentation and the development of active lung disease were against the diagnosis of PSC.

The third report describes a 39 year old woman with metastatic ovarian adenocarcinoma who was thought to have advanced PSC possibly complicated by cholangiocarcinoma. ERC showed diffuse involvement of the intrahepatic biliary tree with multifocal strictures, and involvement of the hepatic duct bifurcation. The extrahepatic ducts were uninvolved, however. Despite a thorough workup, no evidence of malignancy could be found prior to laparotomy for liver transplantation. Vilgrain *et al.*[11] recently reported on three patients with metastatic adenocarcinoma who presented with obstructive cholangiopathy (*Table 6.1*). Cholangiography in all cases showed displacement and distortion of intrahepatic bile ducts with strictures simulating PSC. In two patients, histological examination showed periductal fibrosis or inflammation. Our patient did in fact have an atypical course for PSC characterised by worsening right upper quadrant pain, severe vomiting and rapid weight loss. This clinical presentation could be compatible with cholangiocarcinoma complicating PSC. The lack of extrahepatic duct involvement was against the diagnosis of PSC, although by no means excluded it. The initial pathological diagnosis of benign cystadenomas of the ovaries two years prior to this illness at another institution was obviously misleading. A critical review of the ovarian histology should have led to earlier diagnosis in this instance.

The characteristic cholangiographic findings in PSC consist of multifocal strictures involving intra- and extrahepatic bile ducts with focal areas of dilatation, giving a so-called "beaded appearance".[12,13] This picture may however be closely mimicked by malignant hepatobiliary infiltration due to HES, LCH or metastatic adenocarcinoma. Other malignant tumours that may rarely produce a similar cholangiographic picture include lymphoma,[14] carcinoma of the gallbladder[15] and prostate,[16] and squamous

carcinoma of the liver.[17] The pathogenesis of the cholangiographic findings may be due to biliary distortion by tumor cells, or else due to bile duct injury with resultant scarring. Inflammatory mediators released by eosinophils (eg. major basic protein, eosinophil cationic protein) or histiocytes may have contributed to the biliary injury and scarring seen in these patients.[18] HES and LCH both follow an unpredictable course with relapses and remissions. The abnormal cell types may thus be absent from a liver biopsy specimen which may then show only fibrotic scarring. It may be necessary to biopsy other involved organs, such as bone marrow or lung, in order to diagnose these malignant disorders.

The typical patient with PSC is a young male who has concurrent inflammatory bowel disease, usually ulcerative colitis.[19] The clinical picture is generally that of insidious cholestasis which is slowly progressive, unless complicated by the development of cholangiocarcinoma. Many disorders may mimick PSC, including malignant hepatobiliary infiltration other than cholangiocarcinoma. PSC is a diagnosis that can be made with confidence in the appropriate clinical setting, but remains one of exclusion.

6.4 References

1. Rosen CB, Nagorney DH. Cholangiocarcinoma complicating primary sclerosing cholangitis. *Semin Liver Dis* 1991;11:26-30.

2. Rosen CB, Nagorney DH, Wiesner RH. Cholangiocarcinoma complicating primary sclerosing cholangitis. *Ann Surg* 1991;213:21-25.

3. Lemmer ER, Robson SC, Jaskiewicz J, Krige JEJ. Brief report: Malignant cholangiopathy mimicking primary sclerosing cholangitis. *J Clin Gastroenterol* 1993;16(in press).

4. Fauci AS, Harley JB, Roberts WC, Ferrans VJ, Gralnick HR, Björnson BH. The idiopathic hypereosinophilic syndrome. *Ann Int Med* 1982;97:78-92.

5. Scheurlen H, Mörk H, Weber P. Hypereosinophilic syndrome resembling chronic inflammatory bowel disease with primary sclerosing cholangitis. *J Clin Gastroenterol* 1992;14:59-63.

6. Neeman A, Kadish U. Marked eosinophilia in a patient with primary sclerosing cholangitis. *Am J Med* 1987;83:378-379.

7. Chu T, D'Angio GT, Favara B, Ladish S, Nesbit M, Pritchard J. Histiocytosis syndromes in children. *Lancet* 1987;1:208-209.

8. Romp DM. Langerhans-cell histiocytosis. *N Engl J Med* 1987;16:747-748.

9. Thompson HH, Pitt HA, Lewin RJ, Longmire WP. Sclerosing cholangitis and histiocytosis X. *Gut* 1984;25:526-530.

10. Grosfeld JL, Fitzgerald JF, Wagner VM, Newton WA, Bachner RL. Portal hypertension in infants and children with histiocytosis X. *Am J Surg* 1976;131:108-113.

11. Vilgrain V, Erlinger S, Belghiti J, Degott C, Menu Y, Nahum H. Cholangiographic appearance simulating sclerosing cholangitis in metastatic adenocarcinoma of the liver. *Gastroenterology* 1990;99:850-853.

12. Chapman RWG, Marborgh BA, Rhodes JM, Summerfield JA, Dick R, Scheuer PJ, Sherlock S. Primary sclerosing cholangitis: A review of its clinical features, cholangiography and hepatic histology. *Gut* 1980;21:870-877.

13. Wiesner RH, LaRusso NF. Clinicopathologic features of the syndrome of primary sclerosing cholangitis. *Gastroenterology* 1980;79:200-206.

14. Friedman AC. Cholangiography of metastatic disease and lymphoma/leukemia. In: Friedman AC, ed. *Radiology of the liver, bilary tract, pancreas and spleen.* Baltimore: Williams and Wilkins,1987:3215-3224.

15. Plein K, Czichos E, Gasch J, Hotz J. Imitation einer primar sklerosierenden Cholangitis durch ein infiltrierend Wachsendes Adenokarsinom, ausgehend von der Gallenblasse. *Med Clin* 1990;85:591-594.

16. Taylor J, Lindor K. Metastatic prostate cancer simulating primary sclerosing cholangitis. *J Clin Gastroenterol* 1993;16:143-145.

17. Clements D, Newman P, Etherington R, Lawrie BW, Rhosed J. Squamous carcinoma in the liver. *Gut* 1990;31:1333-1334.

18. Weller PF. The immunobiology of eosinophils. *N Engl J Med* 1991;324:1110-1118.

19. LaRusso NF, Wiesner RH, Ludwig J, MacCarthy RL. Primary sclerosing cholangitis. *N Engl J Med* 1984; 310: 899-903.

Figure 6.1 ERC of case 1 demonstrating marked irregularity of the intrahepatic bile ducts suggestive of primary sclerosing cholangitis.

Figure 6.2 ERC of case 3 demonstrating diffuse narrowing and irregularity of the intrahepatic bile ducts with involvement of the hepatic duct bifurcation. The extrahepatic duct was however not involved.

Table 6.1 Clinical details of 11 cases of malignant obstructive cholangiopathy mimicking primary sclerosing cholangitis.

Case Report	Age (Yrs)	Sex	Diagnosis	Associated Clinical features	Liver Histology	Treatment
1. Scheurlen et al[5]	28	M	Hypereosinophilic syndrome	Eosinophilic colitis, recurrent angioedema	Portal eosinophilic infiltration	Steroids, hydroxyurea
2. Lemmer et al[3]	16	M	Hypereosinophilic syndrome	Chronic colitis, fever, lymphadenopathy	Portal eosinophilic infiltration	Steroids, combination chemotherapy
3. Thompson et al[9]	44	F	Histiocytosis X	Diabetes insipidus, eosinophilic granuloma	Eosinophilic granuloma of bile duct	Steroids, vinblastine, radiotherapy
4. Thompson et al[9]	65	M	Histiocytosis X	Diabetes insipidus	Biliary cirrhosis	Choledochojejunostomy
5. Thompson et al[9]	17	F	Histiocytosis X	Histiocytosis of nodes, lung & skull	Biliary cirrhosis	Choledochojejunostomy, steroids
6. Lemmer et al[3]	10	M	Langerhans-cell histiocytosis	Histiocytosis of lung, hypersplenism	Hepatic fibrosis	Nil specific
7. Vilgrain et al[11]	64	F	Colonic carcinoma	Colonic carcinoma, liver metastases	Metastatic colonic carcinoma	Resection of liver metastasis
8. Vilgrain et al[11]	67	M	Pancreatic adenocarcinoma	Pancreatic carcinoma, weight loss	Metastatic pancreatic carcinoma	Nil specific
9. Vigrain et al[11]	63	M	Pancreatic adenocarcinoma	Pancreatic carcinoma, weakness	Massive invasion of bile ducts	Nil specific
10. Lemmer et al[3]	39	F	Ovarian adenocarcinoma	Severe weight loss, vomiting	Metastatic ovarian cystadenocarcinoma	Combination chemotherapy
11. Taylor et al[16]	71	M	Prostatic carcinoma	Prostatic carcinoma, obstructive jaundice	Metastatic prostatic adenocarcinoma	Leuprolide

CHAPTER 7: REVIEW AND CONCLUSIONS

7.1. Natural history

The last decade has seen major advances in the understanding of many aspects of primary sclerosing cholangitis (PSC).[1] PSC is diagnosed much more frequently with the advent of ERCP, and is no longer considered to be a rare disease.[2] The diagnostic features of PSC have been described in more detail,[3,4] and its natural history better defined.[5,6] As the finding of associated ulcerative colitis is an important confirming point in the diagnosis, all patients with newly diagnosed PSC should undergo colonoscopy, even in the absence of any bowel symptoms. Patients with PSC who have a serum bilirubin level persistently raised above 80μmol/l are likely to have a poor outcome, and should be referred to a Liver Centre for consideration for suitability for, and assessment of timing of liver transplantation. Although most symptomatic patients will progress, the clinical course of PSC is highly variable and a few patients appear to follow a genuinely benign course.[7] This variability and unpredictability may relate to factors in addition to progressive fibrotic biliary stricturing, such as recurrent bacterial cholangitis, concurrent biliary sludge or stones, toxic effects of retained bile salts, and the development of cholangiocarcinoma. Furthermore, it has been our experience that the clinical condition of young women with PSC deteriorates markedly during pregnancy with increasing jaundice and episodes of sepsis. Asymptomatic PSC patients, on the other hand, may experience many years of quiescence despite markedly abnormal cholestatic liver function tests and diffuse extensive biliary stricturing demonstrated at cholangiography.[8-10] These patients may have a milder form of the disease. Alternatively, PSC patients may have a long asymptomatic lag phase followed by a phase of progressive worsening symptoms, somewhat analogous to primary biliary cirrhosis.[11] Clearly long-term follow-up studies of asymptomatic PSC patients are needed in order to resolve this important issue.

7.2. Aetiology

Although the aetiology of PSC remains unknown, genetic and immunological factors appear important. In this context, the close association of HLA DRw52a with the susceptibility to develop PSC is intriguing.[12] HLA DRw52a encodes a protein with a leucine residue at position 38 of the DR B chain.[13] Position 38 is thought to be located in the base of the peptide binding groove of the HLA DR molecule, and it is possible that amino acid substitutions at this site could affect the affinity of peptide binding or DR peptide complex interactions with relevant T cell receptors. The alternative amino acids which can occupy position 38 of DR 3 are alanine and valine, and it would appear that the presence of alanine, associated with HLA DRw53, confers protection from the risk of developing PSC.[13] The close association of HLA class II molecules with PSC suggests that these molecules may play an important role in the regulation of the abnormal immune response which underlies this disease. However, the antigen presented by the HLA molecule remains elusive.

Studies on auto-immune mechanisms in PSC have not yet shown definitive results however, and an infective aetiology could still underlie the pathogenesis of PSC. The HLA data described above could represent susceptibility to an infection rather than variant immune mechanisms. The typical fluctuating clinical course of PSC could be considered as compatible with a chronic re-activating viral infection such as cytomegalovirus (CMV). Infection of the gallbladder by CMV is well documented.[14] Since 1986 infection of the bile ducts with CMV has been increasingly recognised in patients with the acquired immunodeficiency syndrome (AIDS). The development of sclerosing cholangitis in many of these patients ("AIDS sclerosing cholangitis"), with cholangiographic features very similar to classical idiopathic PSC is of great interest.[15] Further evidence of CMV-induced biliary damage is the high incidence of a chronic form of hepatic rejection characterised by loss of intralobular and small bile ducts ("vanishing bile ducts") in patients following orthotopic liver transplantation

complicated by hepatic CMV infection.[16] Direct evidence of CMV infection in PSC came from a study by Mason *et al.*[17] which detected CMV-DNA in the liver tissue of 7/7 PSC patients but in only 5/20 controls. However, Mehal *et al.*[18] were unable to confirm these findings using a highly sensitive polymerase chain reaction (PCR) based assay for CMV-DNA. They studied 37 PSC and 19 control samples of formalin-fixed and paraffin-embedded hepatobiliary tissue. The lack of CMV-DNA in 35 of 36 PSC samples amplified was felt to effectively rule out any significant CMV reactivation in their group and suggested that CMV replication and reactivation were not responsible for the progression of PSC. Personal communications with Mason subsequently suggested methodological difficulties with the published abstract (S.C. Robson; Nov 1992, AASLD).

In Cape Town, we have been collecting samples of serum, urine and tissue from all PSC patients seen. These samples have been stored frozen at -70° and in liquid nitrogen for future research into the genetic, immunologic and infective mechanisms underlying PSC. At present the bank of samples consists of serum (24 patients), urine (24 patients), liver biopsy specimens (16 patients), bile (4 patients), and large amounts of hepatobiliary tissue from transplanted PSC livers (3 patients).

A critical issue in the understanding of the pathogenesis of PSC is the close association of this unusual disease with ulcerative colitis. A previously attractive hypothesis related this association to increased colonic mucosal permeability in regions of high luminal concentrations of anaerobic bacteria (as may occur in chronic ulcerative colitis). Increased uptake of bacteria, bacterial products (endotoxin, peptidoglycan-polysaccharide) or inflammatory mediators (interleukin-1, tumour necrosis factor) into the portal vein could lead to hepatobiliary injury in a genetically susceptible host. In this regard Lichtman *et al.*[19,20] recently reported on an experimental model of hepatobiliary inflammation associated with small intestinal overgrowth of anaerobic bacteria. Surgical creation of a self-filling blind loop in the jejunum of genetically

susceptible rats led to hepatomegaly, increased aspartate transaminase levels, increased bile flow, and chronic periportal inflammation characterised by mononuclear cells and occasional neutrophils surrounding bile ducts, proliferation of small bile ducts and fibrosis. Cholangiography demonstrated tortuosity and irregularity of the intrahepatic ducts, and ectasia of the extrahepatic bile duct. Inbred rat strains exibited differential susceptibility to hepatobiliary inflammation: Lewis rats developed lesions two to four weeks after creation of a blind loop, Wister rats after twelve weeks, and Buffalo and Fischer (MHC compatible with Lewis) rats failed to develop lesions in up to six months of observation despite equal luminal bacterial concentrations. Inflammation apeared to be the result of systemic absorption of peptidoglycan-polysaccharide polymers from intestinal anaerobic bacteria.[21] A negative point to this hypothesis is the lack of effect of colectomy on the natural history of PSC in patients with this disease.[22]

7.3. Antibiotic therapy

In the abovementioned experimental model of small bowel bacterial overgrowth hepatobiliary inflammation can be prevented by metronidazole, tetracycline (but not gentamicin or polymixin B)[23] and mutanolysin,[24] an enzyme that degrades peptidoglycan. Like PSC, the experimental hepatobiliary inflammation did not respond to prednisone, ursodeoxycholic acid, methotexate or cyclosporine A. Long term antibiotic therapy has not been tested in PSC patients in a controlled fashion. Of anecdotal interest however is that two PSC patients followed in Cape Town have remained well on cyclical courses of co-trimoxazole (2 tablets bd for 5 days of the month) after five and nine years respectively (unpublished observation). Prophylactic antibiotic therapy was initially commenced as prophylactic therapy for recurrent bouts of bacterial cholangitis in the two patients. It is thus uncertain whether the possible beneficial effect of co-trimoxazole observed in these patients has been due to the prevention of further episodes of bacterial cholangitis or the treatment of an underlying pathogenetic mechanism of PSC. In the light of these findings a protocol for a

proposed controlled trial of co-trimoxazole in the treatment of PSC in Cape Town has been drawn up (see Appendix A). Anticipated difficulties with such a trial include the long and unpredictable natural history of PSC and the relatively small number of PSC patients seen at only one Liver Centre, and discussions to extend the study to Johannesburg need to be continued.

7.4. Liver transplantation

Currently orthotopic liver transplantation is the therapy of choice for patients with end-stage liver disease due to PSC.[25,26] Currently in 1993 five patients with advanced PSC are awaiting liver transplantation in Cape Town and three patients have undergone this procedure. Although statistical survival models may be helpful, the decision regarding the selection and timing of therapeutic intervention with liver transplantation for PSC requires sound and individualised clinical judgement.[27] Palliative biliary drainage operations should be avoided in PSC patients as such surgery may compromise future liver transplantation.[26,28] Unfortunately, liver transplantation for PSC is fraught with problems including diffuse biliary stricturing and ductopaenic rejection, which appear to occur at a higher frequency in this condition.[29-31] Ultimately more effective medical therapies and prophylactic measures are needed for this fascinating and enigmatic condition.

7.5. References

1. Chapman RW. Aetiology and natural history of primary sclerosing cholangitis: A decade of progress? *Gut* 1991;32:1433-1435.

2. White TT, Hart MJ. Primary sclerosing cholangitis. *Am J Surg* 1987;153:439-443.

3. Chapman RW, Arborgh BA, Rhodes JM, et *al*. Primary sclerosing cholangitis: A review of its clinical features, cholangiography and hepatic histology. *Gut* 1980;21:870-877.

4. Wiesner RH, LaRusso NF. Clinicopathologic features of the syndrome of primary sclerosing cholangitis. *Gastroenterology* 1980;79:200-206.

5. Wiesner RH, Grambsch PB, Dickson ER, Ludwig J, MacCarty RL, Hunter EB. Primary sclerosing cholangitis: Natural history, prognostic factors and survival analysis. *Hepatology* 1989;10:430-436.

6. Farrant JM, Hayllar, Wilkinson ML, *et al*. Natural history and prognostic variables in primary sclerosing cholangitis. *Gastroenterology* 1991;100:1710-1717.

7. Farrant JM, Williams R. Natural history and prognosis in primary sclerosing cholangitis. *Eur J Gastroenterol Hepatol* 1992;4:272-275.

8. Chapman RW, Burroughs AK, Bass NM, Sherlock S. Longstanding asymptomatic primary sclerosing colangitis: Report of three cases. *Dig Dis Sci* 1981;26:778-782.

9. Aadland E, Schrumpf E, Fausa O, *et al.* Primary sclerosing cholangitis: A long-term follow-up study. *Scand J Gastroenterol* 1987;22:655-664.

10. Lemmer ER, Robson SC, Wright JP, Girdwood AH, Bornman PC. Asymptomatic primary sclerosing cholangitis in association with inflammatory bowel disease (letter). *J Clin Gastroenterol* 1993;16 (in press).

11. Neuberger JM. Predicting the prognosis of primary biliary cirrhosis. *Gut* 1989;30:1519-1522.

12. Prochazka EJ, Terasaki PI, Parks MS, Goldstein LI, Busitil RW. Association of primary sclerosing cholangitis with HLA DRw52a. *N Engl J Med* 1990;322:1842-1844.

13. Farrant JM, Doherty DG, Donaldson PT, *et al.* Amino acid substitutions at position 38 of the DR ß polypeptide confer susceptibility to and protection from primary sclerosing cholangitis. *Hepatology* 1992;16:390-395.

14. Blumberg SR, Kelsey P, Perrone T, Dickersin R, Laquaglia M, Ferruchi J. Cytomegalovirus- and cryptosporidium-associated acalculous gangrenous cholecystitis. *Am J Med* 1984;76:1118-1123.

15. Cello JP. Human immunodeficiency virus-associated biliary tract disease. *Semin Liver Dis* 1992;12:213-218.

16. O'Grady JG, Alexander GJM, Sutherland S, *et al.* Cytomegalovirus infection and donor/recipient antigens: Interdependent co-factors in pathogenesis of vanishing bile duct syndrome after liver transplantation. *Lancet* 1988;i:302-305.

17. Mason AL, Rosen G, White H, Wick M, Gelb LD, Perrilo RP. Detection of cytomegalovirus DNA in the liver of patients with primary sclerosing cholangitis by the polymerase chain reaction (abstract). *Hepatology* 1991;14:91A.

18. Mehal WZ, Hattersley AT, Chapman RW, Fleming KA. A survey of cytomegalovirus DNA in primary sclerosing cholangitis using a sensitive polymerase chain reaction based assay. *J Hepatol* 1992;15:396-399.

19. Lichtman SN, Sartor RB, Keku J, Schwab JH. Hepatic inflammation in rats with experimental small bowel bacterial overgrowth. *Gastroenterology* 1990;98:414-423.

20. Lichtman SN, Keku J, Clark RL, Schwab JH, Sartor RB. Biliary tract disease in rats with experimental small bowel bacterial overgrowth. *Hepatology* 1991;13:766-772.

21. Lichtman SN, Keku J, Schwab JH, Sartor RB. Evidence for peptidoglycan absorption in rats with experimental small bowel bacterial overgrowth. *Infection Immunity* 1991;59:555-562.

22. Cangemi JR, Wiesner RH, Beaver SJ, *et al.* Effect of proctocolectomy for chronic ulcerative colitis on the natural history of primary sclerosing cholangitis. *Gastroenterology* 1989;96:790-794.

23. Lichtman SN, Keku J, Schwab JH, Sartor RB. Hepatic injury associated with small bowel bacterial overgrowth in rats is prevented by metronidazole and tetracycline. *Gastroenterology* 1991;100:513-519.

24. Lichtman SN, Okuruwa EE, Keku J, Schwab JH, Sartor RB. Degradation of endogenous bacterial cell wall polymers by the muralytic enzyme mutanolysin prevents hepatobiliary injury in genetically susceptible rats with experimental intestinal bacterial overgrowth. *J Clin Invest* 1992;90:1313-1322.

25. Langnas AN, Grazi FL, Stratta RJ, *et al.* Primary sclerosing cholangitis: The emerging role for liver transplantation. *Am J Gastroenterol* 1990;85:1136-1141.

26. Robson SC, Kahn D, Krige JEJ, Lemmer ER. Primary sclerosing cholangitis (letter). *S Afr Med J* 1991;80:59-60.

27. Wiesner RH, Porayko MK, Dickson ER, *et al.* Selection and timing of liver transplantation in primary biliary cirrhosis and primary sclerosing cholangitis. *Hepatology* 1992;16:1290-1299.

28. Ismail T, Angrisani L, Powell JE, *et al.* Primary sclerosing cholangitis: Surgical options, prognostic variables and outcome. *Br J Surg* 1991;78:564-567.

29. Catalano MF, Ferguson DR, Carey W, Broughan T, Vogt D. Liver retransplantation rate is higher in primary sclerosing cholangitis (abstract). *Hepatology* 1992;16(suppl):275A.

30. Letourneau JG, Day DL, Hunter DW, *et al.* Biliary complications after liver transplantation in patients with pre-existing primary sclerosing cholangitis. *Radiology* 1988;167:349-351.

31. Crippin JS, Carlen SL, Goldstein RM, Husberg BS, Klintmalm G. Ductopaenic rejection : Increased risk in primary sclerosing cholangitis. (abstract). *Hepatology* 1991;16(suppl):276A.

APPENDIX A: PROTOCOL FOR PROPOSED BACTRIM TRIAL

A therapeutic trial to evaluate the efficacy of long term oral co-trimoxazole (Bactrim, Roche^{R}) in the treatment of primary sclerosing cholangitis.

Pricipal Investigator: E. Lemmer
Associate Investigators: P.C. Bornman, S.C. Robson, J.P. Wright, J.E.J. Krige, A. Girdwood, H. Bloch.

1. Introduction

Primary sclerosing cholangitis (PSC) is an uncommon inflammatory disorder of unknown cause characterised by segmental or diffuse fibrosis of the hepatobiliary system. Although the natural history is variable and unpredictable, progression is usually relentless with the development of biliary cirrhosis, portal hypertension and liver failure. The strong association with idiopathic inflammatory bowel disease, especially ulcerative colitis, suggests a causal relationship. Both diseases may be the result of a persistently abnormal immune response to gut derived bacterial antigens. Theoretically, elimination of these bacterial antigens from the gut might interrupt this postulated pathogenic process.

There is anecdotal evidence of a favorable response to the use of long term oral co-trimoxazole (Bactrim, Roche^{R}) in two patients with PSC who did not have recurrent bouts of fever (P.C. Bornman: personal communication). This form of therapy has been introduced in selected patients over the last 15 to 18 months with apparently favourable responses. To date however there have been no controlled studies examining the effect of antibiotics in patients with PSC. Tetracyclines have previously been found to be ineffective. Antibiotics have been used to treat episodes of bacterial cholangitis, or in prophylaxis for patients who have already experienced such insults. In this setting antibiotics may reduce the incidence of recurrent bacterial cholangitis but have no effect on slowing progression of the disease. In the uncontrolled studies cited, patients usually had advanced liver disease, and it is thus possible that only patients with irreversible end-stage liver disease were studied.

The combination of trimethoprim and sulfamethoxazole (co-trimoxazole) results in antimicrobial synergism by sequential inhibition of a common biochemical pathway. Sulfamethoxazole exerts its antibacterial effect by competing with *p*-aminobenzoic acid

(PABA) to prevent the formation of 7,8 - dihydropteroate (DHPA). Trimethoprim inhibits dihydrofolate reductase and thus inhibits the production of tetrahydrofolic acid from dihydrofolic acid (DHFA). Bacterial cells generally cannot absorb exogenous folates; thus they are unable to bypass the block created by trimethoprim and sulfamethoxazole. Mammalian cells are protected because they contain a different dihydrofolate reductase which is much less sensitive to trimethoprim, and absorb exogenous folate.

Co-trimoxazole is active against a wide range of gram-negative enteric organisms, including *E.coli, S.typhi, Shigella* spp. and *Enterobacter* spp. Co-trimoxozale has been used in the treatment of bacterial gastroenteritis and also for prophylactic gut decontamination in neutropaenic patients. Theoretically prolonged treatment with co-trimoxazole may be beneficial in patients with PSC by reducing the number of episodes of bacterial cholangitis. In addition, elimination of gut-derived bacterial antigens may affect the underlying pathogenetic process in this disorder.

Bacteria may develop resistance to trimethoprim-sulfamethoxazole synergism. Mechanisms include (a) an altered dihydropteroate synthetase with a decreased affinity for sulfonamides and (b) an altered dihydrofolate reductase with a decreased affinity for trimethoprim. Both mechanisms may be plasmid - mediated.

Co-trimoxazole toxicity is most frequently due to hypersensitivity reactions. Neutropaenia and thrombocytopaenia may occur. However, few instances of marrow depression secondary to the antifolate effect of trimethoprim have been reported. Such toxicity is theoretically reversible with folinic acid.

The aim of this trial is to assess the efficacy of long term co-trimoxazole in the treatment of PSC.

2. Objectives

1. To determine the efficacy of long term oral Bactrim on improvement of symptoms and biochemical markers in patients with PSC.

2. To assess the safety profile of prolonged treatment with Bactrim in patients with PSC.

3. Trial design

This is a therapeutic trial in which patients will be given treatment with co-trimoxazole for 6 months after which they will be followed on no treatment for another 6 months.

4. Patients

a. *Inclusion criteria*

1. Patients with documented primary sclerosing cholangitis, based on cholangiographic findings, together with compatible clinical (eg. ulcerative colitis) and biochemical features.

2. Symptomatic (patients with a predicted survival prognosis of greater than 1 year, and serum bilirubin less than 85 umol/litre.

3. Patients aged between 18 and 70 years.

4. Written or verbal (witnessed) informed consent.

5. Patient is co-operative and can attend regular clinic visits.

b. *Exclusion criteria*

1. Patients with secondary sclerosing cholangitis or other potential causes of liver disease.

2. Patients who have undergone prior surgery with biliary drainage.

3. Patients with known drug allergy to sulphonamides or trimethoprim, or with G6PD deficiency.

4. Patients who are unable to stop disallowed medication at or before the start of the trial (see below).

5. Patients with advanced liver disease complicated by bleeding varices, ascites or hepatic encephalopathy.

c. *Number of patients*

15 consecutive evaluable patients with proven primary sclerosing cholangitis.

5. Treatment

a. *Drugs, formulations and strengths*

Bactrim single strength (trimethoprim 80mg: sulfamethoxazole 400mg) will be supplied by Roche pharmaceuticals.

b. *Dosage regimen*

Patients will be treated with co-trimoxazole for 6 months after which they will be followed on no treatment for another 6 months.

The two treatment regimen will be as follows:

Group A: Bactrim 2 tablets b.d. x 4 weeks, then
1 tablets daily for 5 months.

After 26 weeks therapy will be stopped and patients will be followed for another 6 months.

c. *Concomitant medication*

The following drugs must not be taken by, or administered to, the patient during the trial:

Penicillamine, colchicine, methotrexate or other experimental therapies for PSC. However patients may be treated with drugs such as ursodeoxycholic acid (UDCA) and cholestyramine which modify bile acids. Antibiotics in conventional dosage and duration of therapy may be used for the treatment of episodes of presumed acute bacterial cholangitis which occur despite co-trimoxazole therapy. Drugs necessary for the treatment of associated inflammatory bowel disease (eg corticosteroids, sulfasalazine) are allowed. However, immunosuppressive agents (eg azathioprine, 6-mercaptopurine) may not be used. All concomitant medications taken during the trial must be recorded.

6. Assessments/evaluatons

A medical history will be taken and physical examination performed at entry; thereafter assessments/evaluations will be made at 4 weeks, 3 months, 6 months and 12 months.. Pill counting wil be done as a check on compliance. A liver biopsy will be a prerequisite for entry into this trial.

a. ***Clinical evaluation***

The following clinical parameters will be scored at each visit:

i. pruritus
ii. jaundice
iii. fatigue
iv. Right upper quadrant pain

Scoring will be as follows:

0 = Absent
1 = Mild
2 = Moderate
3 = Severe
4 = Very severe

In addition the following will be recorded at each visit:

i. Number of febrile episodes since last visit
ii. Weight change since last visit
iii. Degree of incapacitation during last month.

At each visit the patient will complete a 10 cm visual analogue scale (VAS) indicating his / her general well being. The limits of this VAS are: "couldn't be worse" and "couldn't be better"!

b. ***Laboratory analysis***

The following serum biochemical markers will specifically be recorded at each visit:

i. Total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, albumin.
ii. Blood cultures when indicated.
iii. Serum pIII peptide will be measured at week 0, 16 and 32 as a marker of fibrogenesis.

c. *Safety evaluations*

A full blood count will be done at each visit to monitor for the development of cytopaenias during therapy. Anaemia or thrombocytopaenia (eg. due to hypersplenism) is not a contraindication to entry into this study.

7. Adverse experiences

All adverse experiences reported during this clinical trial must be recorded by the investigator. Any patient who develops a serious adverse experience (eg. hypersensitivity reaction, cytopaenia) must immediately be withdrawn from the trial.

8. Statistical analysis

Calculation of the sample size is based on an expected 20% decrease in serum bilirubin and pIII peptide following treatment with co-trimoxazole (bilirubin mean/SD stable symptomatic PSC assumed 39/8.8, alpha=0.05, power=80%). The sample will consist of 15 consecutive patients who will act as their own controls.

The primary efficacy parameters are:

1. The number of patients showing a significant reduction of serum bilirubin and p III peptide at the end of treatment

2. The number of patients discontinuing the trial prematurely because of lack of therapeutic effect.

The secondary efficacy parameters are:

1. Pruritus, jaundice, fatigue

2. Febrile episodes, weight change, incapacitation

3. Visual analogue scale

All secondary efficacy parameters will be analysed in an explorative way.

APPENDIX B: LIST OF PUBLICATIONS

Original articles

1. Robson SC, Kahn D, Krige JEJ, Lemmer ER. Primary Sclerosing Cholangitis (letter). *S Afr Med J* 1991;80:59-60.

2. Lemmer ER, Robson SC, Jaskiewicz K, Levitt C, Krige JEJ. Malignant obstructive cholangiopathies. *J Clin Gastroenterol* 1993(in press)

3. Lemmer ER, Bornman PC, Krige JEJ, Wright JP, Beningfield S, Jaskiewicz K, Kirsch RE, Robson SC. Primary sclerosing cholangitis: requiem for biliary drainage procedures? *Arch Surg* 1993(submitted for publication).

4. Lemmer ER, Wright JP, Robson SC, Girdwood AH, Bornman PC. Asymptomatic primary sclerosing cholangitis associated with inflammatory bowel disease (letter). *J Clin Gastroenterol* 1993;16(in press).

Reviews and Chapters in Textbooks

1. Robson SC, Lemmer ER, Hift R. Drug-induced Hepatotoxicity. In: Kirsch RE, ed. *Liver update*. Cape Town: MRC/UCT Liver Research Centre, 1991:137-150.

2. Lemmer ER, Bloch H. Cholestatic liver diseases. *Continuing Medical Education* 1992;10:1521-1530.

3. Lemmer ER. The syndrome of primary sclerosing cholangitis. *Gastroenterology Forum* 1993 (in press).

4. Lemmer ER. Nausea and vomiting during pregnancy. *Gastroenterology Forum* 1992;3:16-18.